University of Southampton

Faculty of Engineering, Science and Mathematics

School of Chemistry

CH Activation and CH_2 Double Activation of Indolines: Towards the Synthesis of Aspidospermidine and Aspidofractinine

By

Sally Whiting

Thesis for the degree of Doctor of Philosophy.

University of Southampton

Abstract

Faculty of Engineering, Science and Mathematics
School of Chemistry

Doctor of Philosophy.

CH Activation and CH_2 Double Activation of Indolines: Towards the Synthesis of Aspidospermidine and Aspidofractinine

By Sally Whiting.

This thesis is concerned with the total synthesis of the two *Aspidosperma* alkaloid natural products, aspidospermidine and aspidofractinine. The two targets have a common pentacyclic molecular framework unique to this class of indole alkaloids.

Aspidospermidine has previously proven an attractive target, with over 20 total syntheses completed. The hexacyclic framework of aspidofractinine has proven more challenging, with only 5 total syntheses to date. These synthetic approaches are discussed in Chapter 1 together with the pharmacological activity exhibited within the *Aspidosperma* alkaloid series.

Chapter 3 details the challenges of installing the first 4 rings of the targets (the ABDE ring system). Ring expansion of a C3 cyclopropyl indolone with an imine, ultimately provided a quick and efficient route to the tetracyclic structure. With the model system realised, Chapter 3 details the synthetic efforts towards an elaborated imine component and its subsequent use in the ring expansion methodology to give our key precursor.

Chapter 4 discusses model systems to prove our key radical translocation step can be achieved. Systems are described that show intramolecular translocation of an aryl radical to C2 of an indoline is a feasible means of elaborating this centre.

Contents

Preface

The research described in this thesis was carried out under the supervision of Prof. D. C. Harrowven at the University of Southampton between October 2004 and October 2007.

No part of this thesis has previously been submitted for a degree.

Acknowledgements

My first and eternal thanks go to Prof. D. C. Harrowven, for his expert supervision, unending optimism and infinite ideas! For your enthusiasm, support and belief in me I will be forever grateful. You have made the last 3 years an amazing experience.

My second “thank you” is for my industrial supervisor Toby Thompson. The three months I spent at AstraZeneca proved to be inspiring for myself and for our project and that inspiration is entirely down to you!

The “Harrowven group”. Thank you to you all for making the lab such a fantastic (if slightly strange....) place to work, I have loved every minute of working with you! Simon and Will - It was starting to feel like this moment would never arrive!! I am so proud of you both! Thanks for sharing a fantastic 3 years in the lab and being an unending source of support. Ian & Dave-for making the Harrowven lab such a wonderful group to join. Phil-for always having a smile on the toughest of days and making me laugh when the going got tough! The group would be a quieter place without you! Kerri & Stephen-for making the lab such a happy place to come back to. Lana and Sarah-for the countless bottles of wine, dancing, gossip and support I will be forever grateful.

To the research support team at Southampton: John & Julie, Joan & Neil, Karl, Tony and Graham. Thanks for keeping things running smoothly and making our job that bit easier!!

To my family and friends: Mum, Dad, Nicola and Joe, your love and belief in me have given me more confidence and inspiration then you will ever know, Thank You!! Bex, Laura, Mish, Claire, Kerry, Katie, Jess, Alison, Jessica, Ellen, thank you for your continued support.

And finally to Nicola, George and Rach – thank you for being my “shining stars”, for sharing the highs and lows, for making me laugh when needed and for giving me the confidence, drive and inspiration to succeed-the drinks are on me!!!

Abbreviations

Ac	acetyl
acac	acetylacetone
AIBN	α,α-azo-*iso*-butyronitrile
aq.	aqueous
Ar	aryl
9-BBN	9-borabicyclononane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOM	benzyloxymethyl
Bu	butyl
Bz	benzoyl
n-BuLi	*n*-butyllithium
cat.	catalytic
CI	chemical ionisation
conc.	concentrated
Δ	reflux
d	days
DCM	dichloromethane
dba	dibenzylidene acetone
DBU	diaza(1,3)bicycle[5.4.0]undecane
DABCO	1,4-diazabicyclo[2.2.2]octane
DEAD	diethyl azodicarboxylate
DIBAL-H	di-*iso*-butylaluminium hydride
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N,N′*-dimethylformamide
DMPU	*N,N′*-dimethylpropyleneurea
DMS	dimethylsulfide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio

EA	ethyl acetate
ee	enantiomeric excess
EI	electron impact
equiv.	equivalents
ES	electrospray
Et	ethyl
ether	diethyl ether
h	hours
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	Hertz
IR	infrared
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
M	molar
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minutes
Mpt	melting point
Ms	mesyl (methanesulfonyl)
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance spectrometry
NPIF	(*o*-nitrophenyl)phenyliodonium fluoride
PCC	pyridinium chlorochromate
Ph	phenyl
PPA	polyphosphoric acid
ppm	parts per million
Pr	propyl
py	pyridine
RSM	recovered starting material
RT	room temperature

TBDMSCl	*tert*-butyldimethylsilyl chloride
TEA	triethylamine
TEOC	trimethylsilylethoxycarbonyl
TES	triethylsilane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosylate (*para*-toluene sulfonyl)
p-TSA	*para*-toluenesulfonic acid
TTF	tetrathiafulvalene
TTMSS	*tris*-(trimethylsilyl)silane
VAZO	1,1′-azobis(cyclohexanecarbonitrile)

Chapter 1–Introduction to aspidospermidine and aspidofractinine.

Background

The *Aspidosperma* alkaloids are the largest group of monoterpenoid indole alkaloids, comprising over 250 members, with unprecedented structural complexity shown throughout the family. The alkaloid family occurs naturally in only a restricted number of plant genera, with the vast majority being isolated from one subgroup (Plumerioideae) of the Apocynaceae family which is widely distributed in the tropical rainforest. The interesting biological activity and structural complexity shown within this group have provided the inspiration for synthetic effort for over 40 years and they remain a focus of extensive research activity in the present day.

The diverse molecular architecture shown throughout the family can be classified into several distinct subgroups which include: quebrachamine **1**, aspidospermidine **2**, vincadifformine **3**, aspidofractinine **4** and the more elaborate vindolinine **5**, meloscine **6**, and kopsine **7** (Figure 1).[1] The vast majority of the *Aspidosperma* alkaloids contain a pentacyclic core exemplified by the aspidospermidine sub-group containing the 6.5.6.6.5 fused ring system.

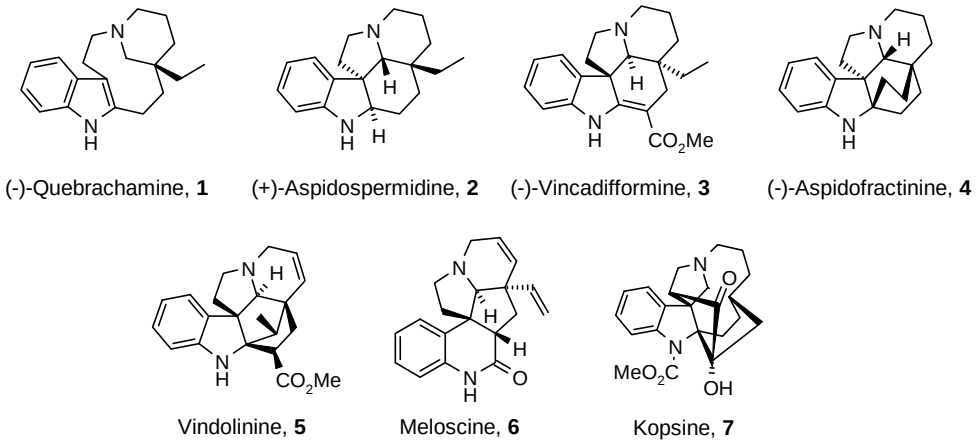
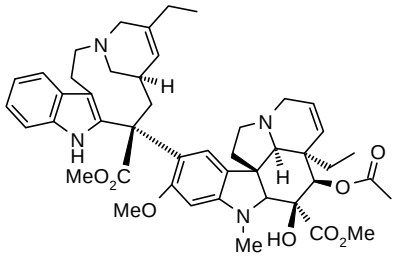


Figure 1: *Aspidosperma* alkaloid sub-groups.

A number of species of the *Aspidosperma* genera are used in folk medicine to treat general fever, whilst others are used specifically against malaria. More recently, interest in the family has been considerable due to the pharmacological activity exhibited by a few of its members. In particular anti-cancer activity is displayed amongst the dimeric indole alkaloids, such as vincristine and vinblastine, which have

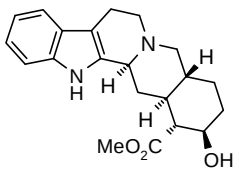
enjoyed early clinical success. Research into this sub-group produced vinorelbine® (navelbine) **8**, a semi-synthetic derivative of vinblastine currently being used as a chemotherapy drug to treat breast and lung cancers (Figure 2).[2] This 'dimeric' indole alkaloid is comprised of two 'monomeric' components that are analogues of quebrachamine and aspidospermidine and highlights the interest in both monomer natural products as individual targets.



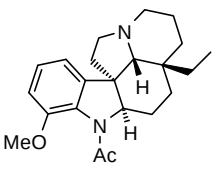
Vinorelbine, **8**

Figure 2: Anti-cancer agent, vinorelbine, **8**.

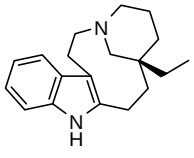
The isolation of quebrachamine **1** was accomplished as early as 1882[3] but its structural features were not elucidated until Witkop and co-workers investigations in 1960.[4] It was the pioneering work of Biemann *et al.* in the 1960's that led to the full structural determination of quebrachamine along with many other alkaloids.[5] The bark of *Aspidosperma Quebracho blanco*, a South American tree located in the northern regions of Argentina, was investigated by Biemann *et al*.[5b] Gas chromatography and mass spectrometry were used to investigate the crude alkaloid mixture obtained from the bark of the tree, leading to the detection of over 20 compounds, 16 of which were isolated in sufficient quantity for structural determination. Amongst these compounds were the known alkaloids yohimbine **9**, aspidospermine **10** and quebrachamine **1** along with the newly discovered aspidospermidine **2** (Figure 3). The mass spectral fragmentation behavior and UV data of the aspidospermine class of alkaloids allowed the structural elucidation of aspidospermidine to be achieved.



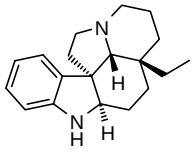
(-)-Yohimbine, **9**



(-)-Aspidospermine, **10**



(-)-Quebrachamine, **1**



(+)-Aspidospermidine, **2**

Figure 3: Alkaloids of *A. Quebracho blanco*.

The targets

Our primary synthetic targets are aspidospermidine **2** and aspidofractinine **4**. Both are structurally complex monoterpenoid *Aspidosperma* indole alkaloids and the parent members of their individual subclass (Figure 4).

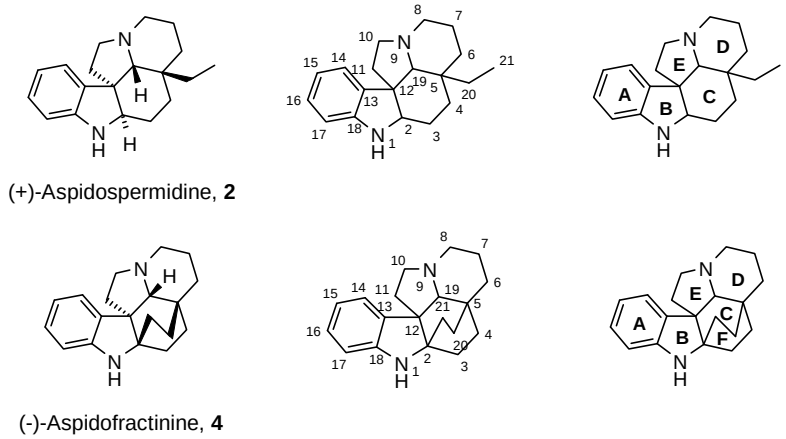


Figure 4: Ring & numbering system[6] of aspidospermidine **2** and aspidofractinine **4**.

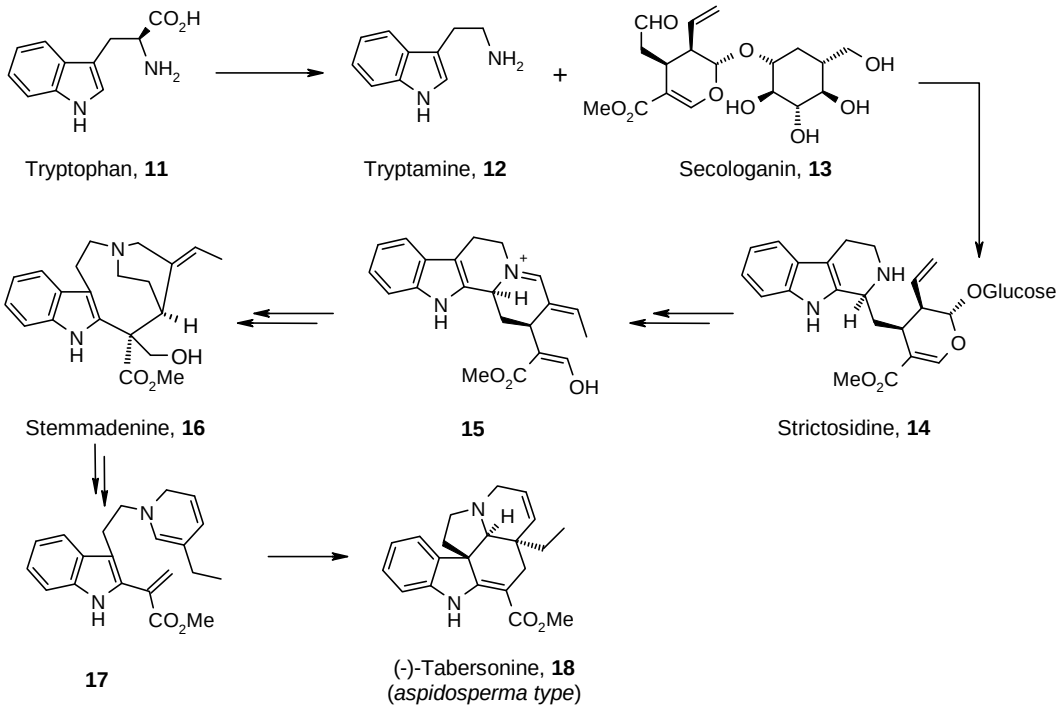
Whilst aspidospermidine **2** and aspidofractinine **4** are to date devoid of significant biological activity, their distinctive framework is found throughout the family of *Aspidosperma* alkaloids and in many *bis*-indole alkaloids which *are* pharmacologically significant. The fascinating molecular architecture of these natural products has inspired significant scientific effort. Both natural products, along with the others in their family, are isolated from the genera *Aspidosperma* from the Apocynaceae family. Aspidospermidine **2** is principally found in *Aspidosperma Quebracho balanco* (Argentina)[5b] and *Rhazya stricta* (Asia)[7] with aspidofractinine **4** isolated from *Aspidosperma refractum* (Brazil)[8] and *Aspidosperma pyrifolium* (Brazil)[9].

Aspidospermidine **2** is the simplest alkaloid to contain the characteristic pentacyclic structure. It is devoid of sensitive functional groups and has consequently been used as the primary target to test the numerous synthetic strategies aimed at this family, resulting in numerous total syntheses. Aspidospermidine **2** is the parent of its subclass, the largest class of *Aspidosperma* alkaloids, with over 140 members; and typifies the core structure of this family with the pentacyclic ABCDE [6.5.6.6.5] ring system (Figure 4). Aspidofractinine **4**, also the parent of its subclass (>30 members), retains this ring system but also has an additional F ring, ABCDEF [6.5.6.6.5.6]. The pentacyclic skeleton of

aspidospermidine **2**, the four contiguous stereogenic centres on ring C and the creation of a tetrasubstituted carbon at the BCE ring junction are significant challenges that need to be realized in order to achieve a total synthesis. Aspidofractinine **4** has the additional challenge of installing the sixth ring.

Biosynthesis

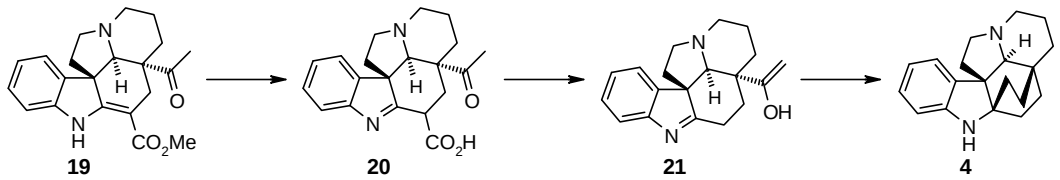
All indole alkaloids are derived from tryptophan **11** and the iridoid secologanin **13**. Tryptophan decarboxylase converts tryptophan **11** to tryptamine **12**, which then undergoes condensation with secologanin **13** to produce strictosidine **14**, the general intermediate of indole alkaloid synthesis (Scheme 1).[10] The Apocynaceae family of plants produces a vast number of indole alkaloids with dramatically differing structures, all of which are obtained by rearrangement of the intermediate strictosidine **14** during secondary metabolism. As early as 1962 Biemann and coworkers postulated the presence of intermediates akin to **15** in the biosynthesis of these natural product systems.[5c] However, the mechanistic pathways of some of these secondary metabolism processes still remain unclear today.



Scheme 1: Proposed biosynthetic pathway for synthesis of *Aspidosperma*-type alkaloids.

It is believed that strictosidine **14** is deglycosylated to a reactive hemi-acetal, which opens to a dialdehyde that is subsequently captured by the secondary amine. Allylic isomerisation then gives the iminium intermediate **15** which undergoes conversion by unknown mechanism to stemmadenine **16**. Dehydration and rearrangement to the acrylic ester **17** allows intramolecular cycloaddition to occur establishing the *Aspidosperma* skeleton, **18** (Scheme 1).

It is believed that the aspidofractinine-type alkaloids are biosynthesized from intermediates akin to **19**. Tautomerism and saponification to **20**, decarboxylation and enol formation (to **21**), facilitate cyclisation to the hexacyclic skeleton giving **4** after reduction of the intermediate ketone (Scheme 2).[11]



Scheme 2: Late stage proposed biosynthetic pathway for synthesis of aspidofractinine-type alkaloids.

Over the past half century numerous approaches to the complex ring systems of the *Aspidosperma* alkaloids have been reported in the literature. Many follow bio-mimetic pathways whilst others use these diverse ring systems as a template on which to develop new synthetic methodologies.

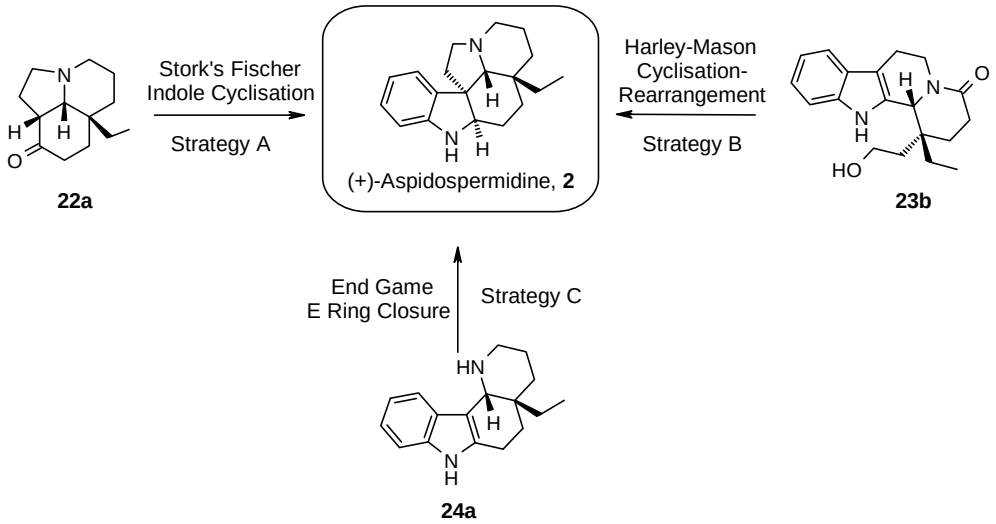
Previous syntheses

Over 20 total syntheses of aspidospermidine **2** have been reported[2,12,13,17-32,34,35,40,41] since Stork and Dolfini's pioneering work on this family in 1963.[12] Only 5 have been reported for aspidofractinine **4**.[36-41] The majority of the synthesis towards aspidospermidine **2** follow one of the following 3 synthetic strategies (Scheme 3):

A – Stork's Fischer indole cyclisation of aminoketone **22a** with phenyl hydrazine.[12]

B – Harley-Mason's rearrangement of **23**.[13]

C – The elaboration of ring E onto the ABCD precursor **24a**.



Scheme 3: Synthetic strategies towards aspidospermidine **2**.

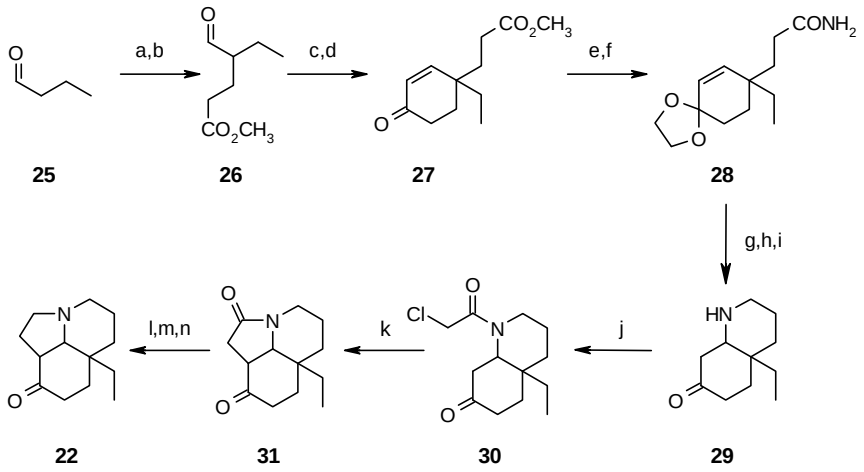
This literature review will discuss each of these strategies in turn, before reporting the more individual syntheses of aspidospermidine **2** and synthetic routes to aspidofractinine **4**. Early syntheses of aspidospermine **10** will be covered where relevant.

Strategy A - Stork and Dolfini's ground-breaking Fischer-Indole approach.

The first successful foray into this class of alkaloids targeted aspidospermine, **10**. In 1963 Stork and Dolfini performed a Fischer-Indole cyclisation between the key tricyclic ketone **22** and *o*-methoxyphenyl hydrazine to install the pentacyclic ring system of the natural product.[12]

The key CDE tricyclic intermediate **22** was prepared according to Scheme 4. Alkylation of the pyrrolidine enamine of butyraldehyde, first with methyl acrylate then with methyl vinyl ketone, induced cyclisation to cyclohexenone **27**. The ketone group was then protected by ketalisation before conversion of the ester moiety into the corresponding amide **28**. $LiAlH_4$ reduction of the amide next released the primary amine which on hydrolysis of the ketal underwent an internal Michael addition to the enone system installing the bicyclic system, **29**.

Ring E was introduced by acylation of **29** with chloroacetyl chloride to give chloroacetamide **30**. Cyclisation was then induced by treatment with potassium *t*-butoxide. The key tricyclic aminoketone **22** was then accessed by ketalisation, lithium aluminium hydride reduction of the amide and subsequent deprotection of the ketone functionality.

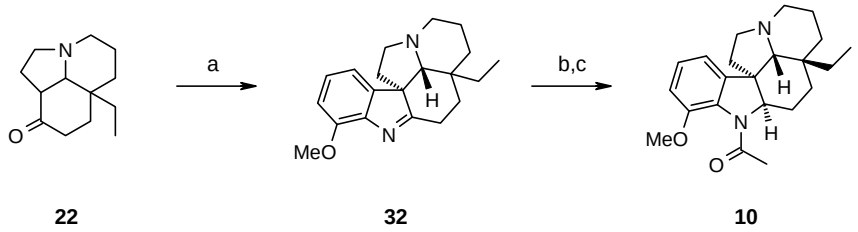


Scheme 4: Synthetic route to key intermediate **22**.[12]

Reagents and conditions: (a) Pyrrolidine, methyl acrylate; (b) AcOH, H_2O, RT, 67% (2 steps); (c) pyrrolidine, methyl vinyl ketone; (d) AcOH, H_2O, Δ, 48% (2 steps); (e) $(CH_2OH)_2$, H^+; (f) NH_3, H_2O; (g) $LiAlH_4$; (h) H_2O, H^+; (i) HO^-; (j) chloroacetyl chloride; (k) *t*-BuOK, benzene; (l) $(CH_2OH)_2$, H^+; (m) $LiAlH_4$; (n) H_2O, H^+.

With aminoketone **22** in hand, the key Fischer-Indole cyclisation was performed. Treatment of the *o*-methoxyphenyl hydrazone of **22** with hot acetic acid

resulted in the formation of indolenine **32**. Stereoselective reduction of the imine then set the C2 stereocentre. Finally, acetylation completed the total synthesis giving aspidospermine **10** (Scheme 5).

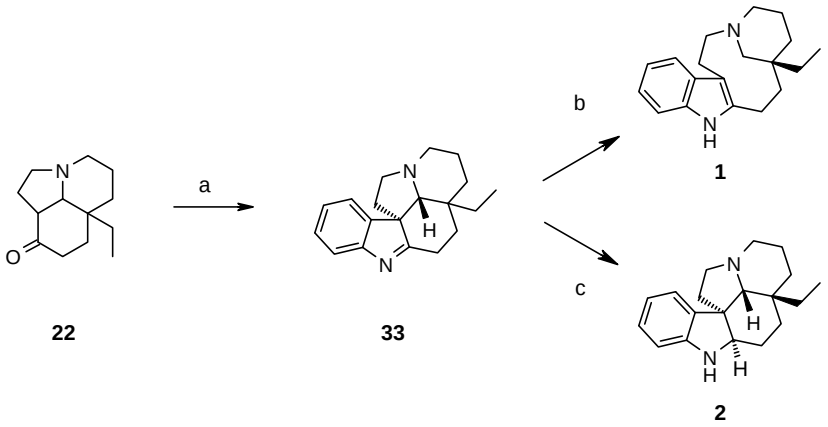


22 **32** **10**

Scheme 5: Fischer-Indole cyclisation and closing stages to aspidospermine **10**.[12]

Reagents and conditions: (a) *o*-methoxy-phenylhydrazine, benzene, Δ then AcOH, Δ; (b) $LiAlH_4$; (c) acetic anhydride.

This synthetic route represents a formal total synthesis of aspidospermidine **2** and also allowed access to quebrachamine **1**, another member of the *Aspidosperma* family. Cyclisation of the phenylhydrazone of **22** to give **33**, followed by reductive cleavage with potassium borohydride gave quebrachamine **1**, while reduction with $LiAlH_4$ furnished aspidospermidine **2** (Scheme 6).



22 **33** **1** **2**

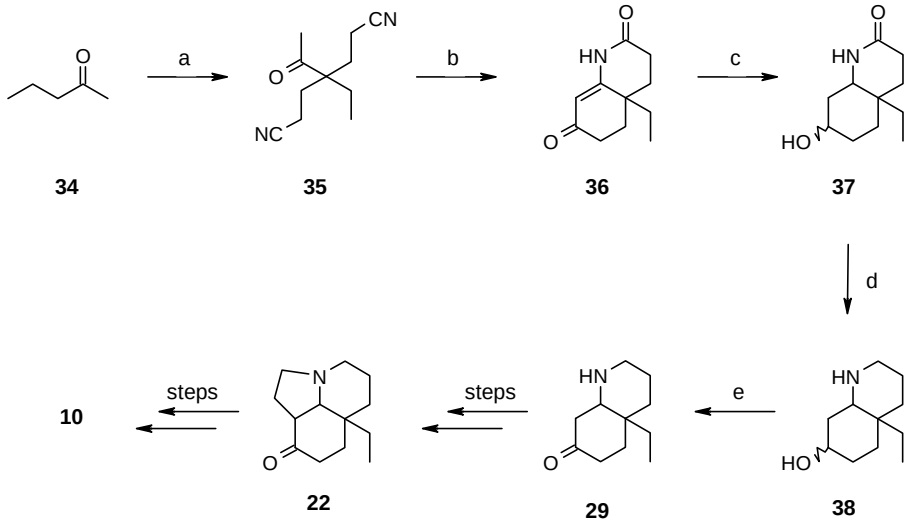
Scheme 6: Closing stages to quebrachamine **1** and aspidospermidine **2**.[12]

Reagents and conditions: (a) Phenylhydrazine, benzene, Δ then AcOH, Δ; (b) KBH_4, KOH, MeOH; (c) $LiAlH_4$, THF, Δ.

Ban's approach towards tricyclic ketone 22.

Two years after Stork's pioneering work, Ban and his co-workers completed their total synthesis of aspidospermine **10**.[14] The route involved an alternative sequence for the preparation of aminoketone **22**, at which point it converged with Stork's original synthesis.[12]

Condensation of 2 molar equivalents of acrylonitrile with methyl *n*-propyl ketone **34** gave **35** which afforded the bicyclic dicarbonyl **36** on treatment with sulfuric acid. Hydrogenation to **37** followed by steps to modify oxidation levels provided bicyclic amino ketone **29**. The synthetic route then converged with Stork's synthesis to insert ring E, then rings A and B to complete the total synthesis of **10** (Scheme 7).

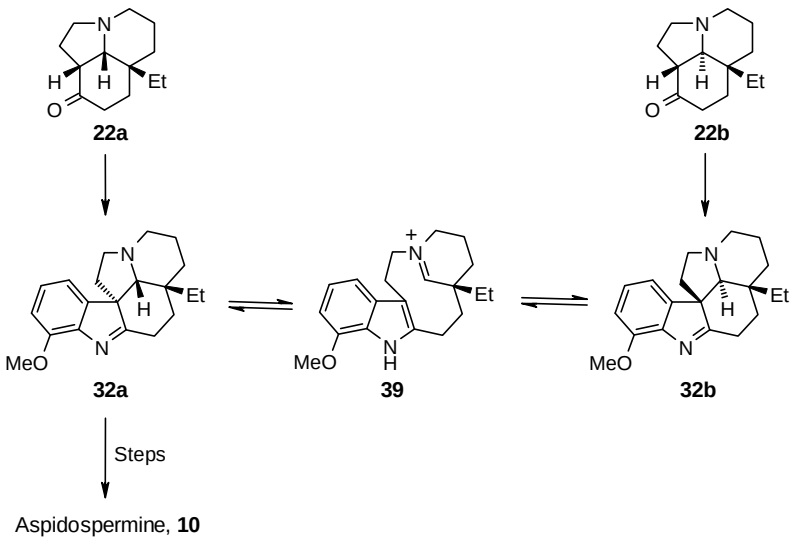


Scheme 7: Synthetic route towards **10**.[14]

Reagents and conditions: (a) 2 equiv. acrylonitrile; (b) 80% H_2SO_4, Δ, 5 min, 80% (2 steps); (c) H_2, Pd, HO^-, 79%; (d) $LiAlH_4$, THF, 75 °C, 20 h, 81%; (e) Oppenauer oxidation, *t*-BuOK, cyclohexanone, 74%.

The physical data obtained by Stork and Ban did not provide an exact match and it was found that Stork's aminoketone **22a** and Ban's aminoketone **22b** were stereoisomeric.[1] Stork's elegant route to the natural product was not dependent on the stereochemistry of this tricyclic intermediate as it was deduced that the indolenine **32a**, formed under the acidic conditions of the Fischer Indole cyclisation, could undergo isomerisation.[1] Reversible Mannich fission of the C12-C19 bond gave the open iminium ion **39** which can conceivably reclose to give either of the possible

isomers **32a** or **32b**. Under equilibrating conditions the most thermodynamically stable arrangement dominates, irrespective of the stereochemistry in the initial aminoketone (**22a** or **22b**), which in the *Aspidosperma* case is the natural one **32a** (Scheme 8). Ban *et al*. later reported the synthesis of the less stable kinetic product **32b** by performing the Fischer Indole cyclisation in formic acid.[15]



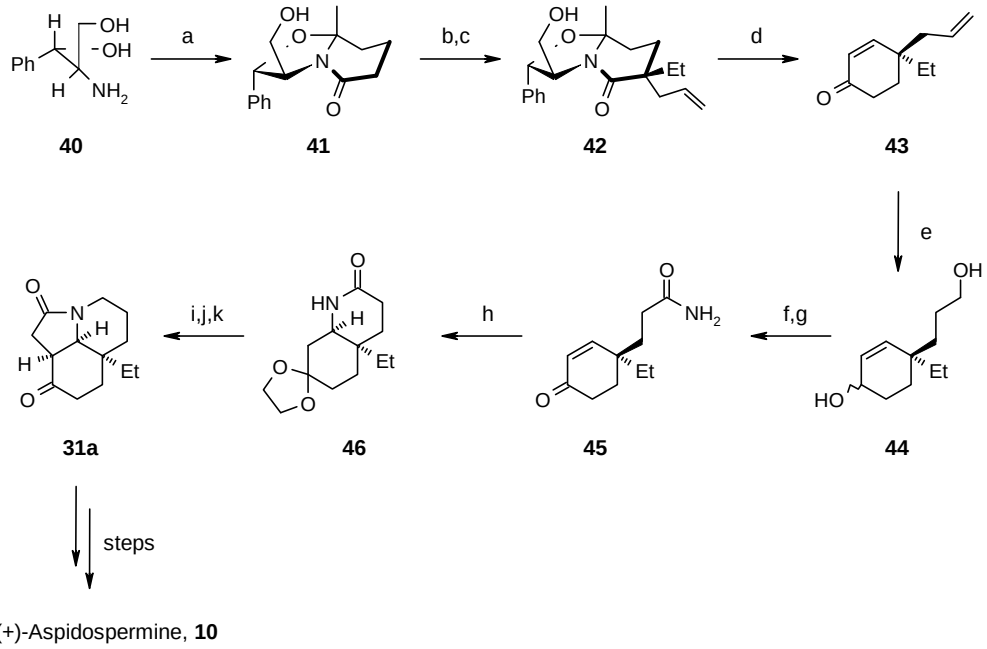
Scheme 8: Equilibration to the natural product arrangement.

Since Stork's first contribution many groups have taken up the challenge of the total synthesis of aspidospermine **10**, aspidospermidine **2** and related family members. Stork and Ban's individual syntheses represent the first entry into this group of the indole alkaloids. Both prepared the tricyclic aminoketone **22** in racemic form before generating the pentacyclic core of the natural product using a Fischer indole synthesis. Many groups have followed this elegant strategy, preparing the key amidoketone intermediate **31** in various ways and completing the total synthesis using Stork's closing sequence.

Meyers' asymmetric synthesis of tricyclic amidoketone 31.

In 1989 Meyers and Berney completed an asymmetric synthesis of the key amidoketone intermediate **31**, and a total synthesis of the unnatural enantiomer, (+)-aspidospermine **10**.[16] The route used chiral bicyclic lactam **41** to set the absolute configuration at C5 of the natural product. With this centre set, the synthesis followed a similar strategy to Stork's in next closing rings D and E.

Meyers' synthesis began by condensing the commercially available aminodiol **40** with a commercially available keto acid to give the chiral bicyclic lactam **41**. This was then alkylated sequentially with ethyl iodide and allyl bromide to give **42** with the allyl group *endo*. Lactam **42** was next transformed into cyclohexenone **43** by treatment with Red-Al followed by acidic hydrolytic cleavage and the terminal olefin hydrated to alcohol **44** using 9-BBN with an oxidative work up. A short sequence of functional group manipulations afforded amide **45** which on heating in benzene with ethylene glycol and *p*-TSA induced closure of ring D to give **46**. Stork's route was then used to incorporate ring E, giving chiral amidoketone **31a**. The synthesis of (+)-aspidospermine **10** was then completed according to Stork's synthesis (Scheme 9).



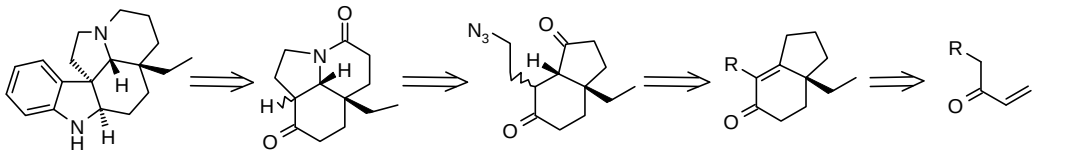
Scheme 9: Meyers' synthesis of (+)-aspidospermine **10**.[16]

Reagents and conditions: (a) $CH_3COCH_2CH_2CH_2CO_2H$, benzene, Δ, 84%; (b) LDA, THF, EtI, 92%; (c) LDA, allyl bromide, 75%; (d) (1) Red-Al, toluene; (2) H_2O, H^+, 77%; (e) 9-BBN, THF, 0 °C, then NaOH, H_2O_2; (f) Jones reagent, acetone, 70% (2 steps); (g) (1) oxalyl chloride, CH_2Cl_2; (2) NH_3, 73%; (h) ethylene glycol, *p*-TSA, benzene, Δ, 85%; (i) (1) $LiAlH_4$, THF, Δ; (2) H_2O, H^+, Δ, 87%; (j) chloroacetyl chloride, NEt_3, benzene, 61%; (k) *t*-BuOK, benzene, 72%.

Overall Meyers' approach gave chiral amidoketone **31a** in 11 steps and 7.4% overall yield from commercially available starting materials.

Aubé's asymmetric synthesis of tricyclic amidoketone 31 and total synthesis of aspidospermidine (2).

Aubé *et al*.[17] proposed the use of an intramolecular Schmidt reaction of azide **47** to simultaneously install ring E and expand ring D in an enantiomerically pure synthesis of the Stork intermediate **31** (Scheme 10). The total synthesis would rely on the azide selectively reacting with the cyclopentanone in **47** in the key Schmidt reaction.

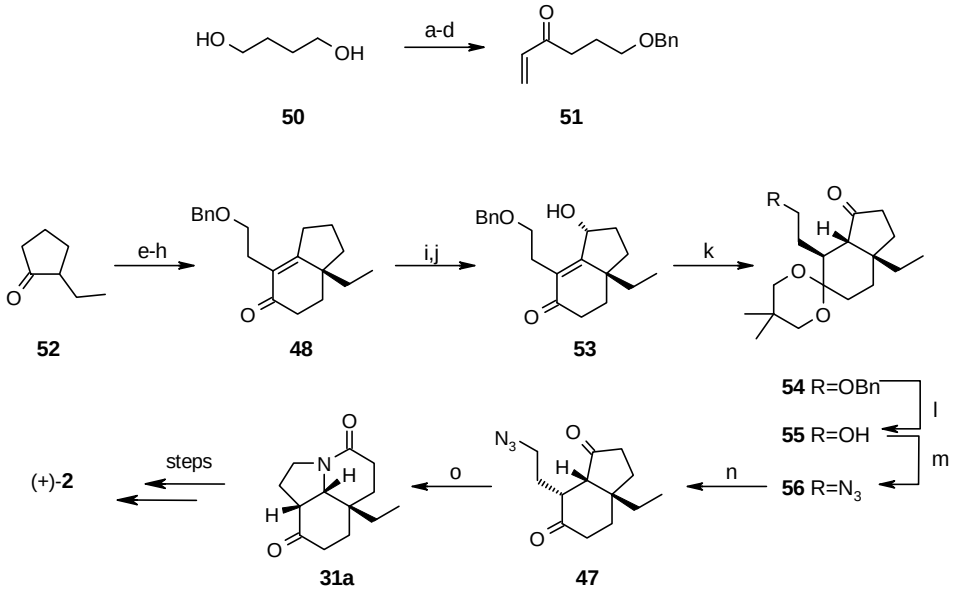


2 **31** **47** **48** R=CH_2CH_2OBn **49** R=CH_2CH_2OBn

Scheme 10. Retrosynthetic strategy employed by Aubé *et al*.[17]

The preparation of enone **48** in an enantiomerically enriched form was achieved using a deracemizing imine alkylation protocol. Cyclopentanone **52** was condensed with (*S*)-α-methylbenzylamine and the resultant enamine condensed with vinyl ketone **51** (prepared in a 4 step process from diol **50**). Acid hydrolysis followed by an intramolecular aldol reaction afforded the bicycle **48**. γ-Oxidation to **53** was followed by ketalisation to **54**, reductive debenzylation to **55** and a Mitsunobu reaction to azide **56**, setting the stage for the crucial step.

The Schmidt reaction of **56** was not successful. However, following deprotection of the ketal to **47**, which also induced isomerization of the side chain to the required α-position, it proceeded smoothly and selectively to give tricyclic lactam **31a** as a single diastereoisomer (84% ee, ≥ 99% ee after recrystallisation). Paralleling Stork in the final stages, amidoketone **31a** was converted in 3 steps to the corresponding ketoamine which underwent Fischer Indole cyclisation to complete the total synthesis of (+)-aspidospermidine **2** (Scheme 11).



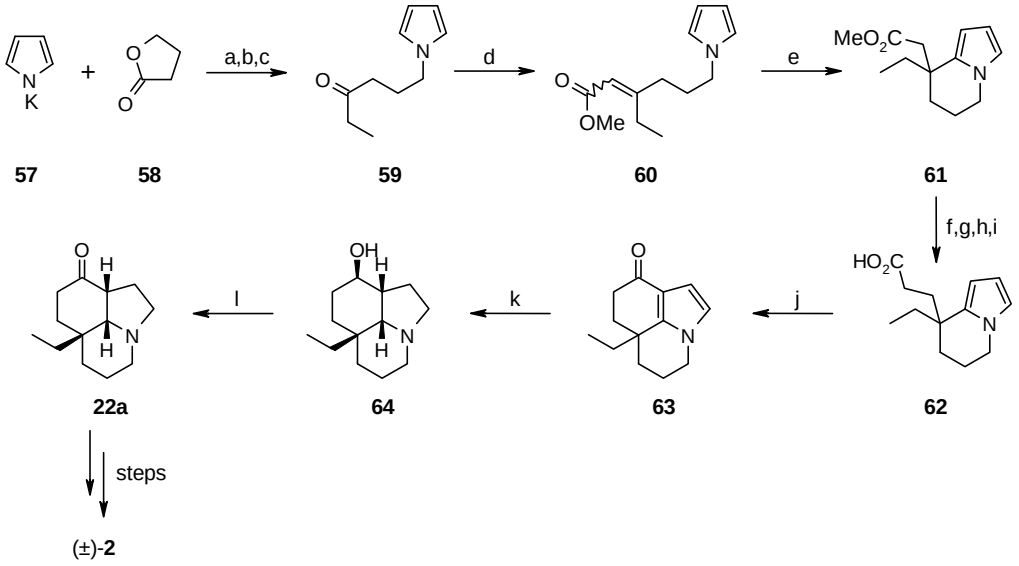
Scheme 11: Aubé's synthesis of (+)-aspidospermidine **2**.[17]

Reagents and conditions: (a) NaH, BnBr, DMF; (b) PCC, CH_2Cl_2; (c) CH_2=CH_2MgBr, THF; (d) CrO_3, H_2SO_4, acetone, 23% (4 steps); (e) (*S*)-α-methylbenzylamine, *p*-TsOH, benzene, reflux, 17 h; (f) **51**, hydroquinone, fused $ZnCl_2$, Et_2O, reflux, 72 h; (g) 10% aq. AcOH, RT, 3 h; (h) NaOMe, MeOH, reflux, 24 h, 49% (4 steps); (i) *p*-TsOH, isopropenyl acetate, reflux, 5 h; (j) oxone, acetone, 3 h, RT, 88% (2 steps); (k) bis(trimethylsilyl)neopentyl glycol, TMSOTf, CH_2Cl_2, 0 °C to RT, 10 h, 69%; (l) H_2, 10 % Pd/C, MeOH, RT, 12 h, 85%; (m) HN_3, PPh_3, DEAD, PhH, 0 °C to RT, 73%; (n) $LiBF_4$, H_2O, MeCN, 70 °C, 18 h, 89%; (o) $TiCl_4$, CH_2Cl_2, 0 °C to RT, 2.5 h, 82%.

In summary, Aubé's approach incorporates a selective Schmidt cyclisation allowing the preparation of enantiomerically pure **31a** in 14 steps from **50**, with a 3.1% overall yield.

Banwell's synthesis of tricyclic amino ketone 22.

In 2002 Banwell and Smith reported a formal total synthesis of (±)-aspidospermidine **2**.[18] Their route exploits the multiple nucleophilic sites on pyrrole at N1, C2 and C3 to assemble the racemic CDE-ring substructure of aminoketone **22** (Scheme 12). This late stage intermediate intersects Ban's earlier synthesis of aspidospermidine **10**.[14]



Scheme 12: Banwell's formal synthesis of (±)-aspidospermidine **2**.[18]

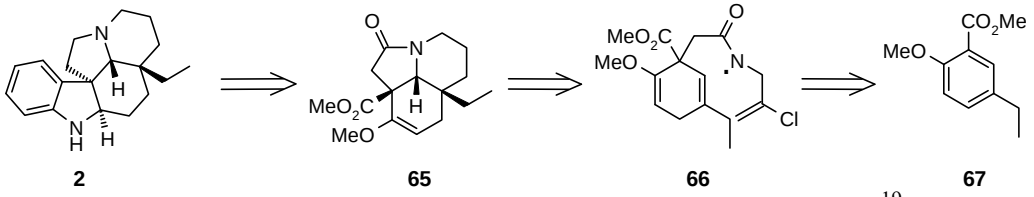
Reagents and conditions: (a) 160 °C, 2 h, 90%; (b) $H_3CNHOCH_3$.HCl, Et_3N, pyridine *N*-oxide disulfide, Bu_3P, CH_2Cl_2, 18 °C, 16 h, 87%; (c) (1) EtMgBr, Et_2O, 18°C, 1 h, (2) 0.3 M aq. $KHSO_4$ (excess), −40 °C, 0.1 h, (3) $NaHCO_3$ (excess), −40 °C to 18 °C, 100%; (d) NaH (2 equiv.), $(EtO)_2POCH_2CO_2Me$ (2 equiv.), THF, 18 °C, 48 h, 77%; (e) $AlCl_3$ (5 equiv.), Et_2O, 18 °C, 5 h, 83%; (f) DIBAL-H (2 equiv.), CH_2Cl_2, −78 °C, 0.16 h, 75%; (g) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0−18 °C, 1 h, 95%; (h) NaCN (5 equiv.), DMPU, 18 °C, 48 h, 91%; (i) KOH (26 equiv.), H_2O, MeOH, Δ, 16 h, then aq. HCl, 88%; (j) HCl (excess of a 5 M solution), 18 °C, 1 h, 72%; (k) H_2, Pt_2O (cat.), AcOH, 18 °C, 18 h; (l) Dess-Martin periodinane (3 equiv.), CH_2Cl_2, 0−18 °C, 1 h , 28% over 2 steps.

The potassium salt of pyrrole **57** was heated with γ-butyrolactone **58** to give the product of *N*-alkylation. The resultant acid was then converted to a Weinreb amide which was treated with ethyl magnesium bromide to give ethyl ketone **59**. A Wadsworth-Emmons olefination next gave **60**, which underwent an intramolecular Michael-type addition to bicyclic ester **61**. One carbon homologation to acid **62** was followed by a Friedel-Crafts cyclisation to give tricycle **63**. Careful hydrogenation of **63** gave alcohol **64** which in turn was oxidized to the tricyclic aminoketone **22a**.

The late stage aminoketone **22a** was achieved in 12 steps from pyrrole in 5.8% overall yield. The racemic synthesis incorporates an intramolecular Michael-type addition and a Friedel-Crafts type cyclisation to a pyrrole but is let down by a low yielding hydrogenation step **63→64**.

Zard's radical cyclisation approach to (±)-aspidospermidine.

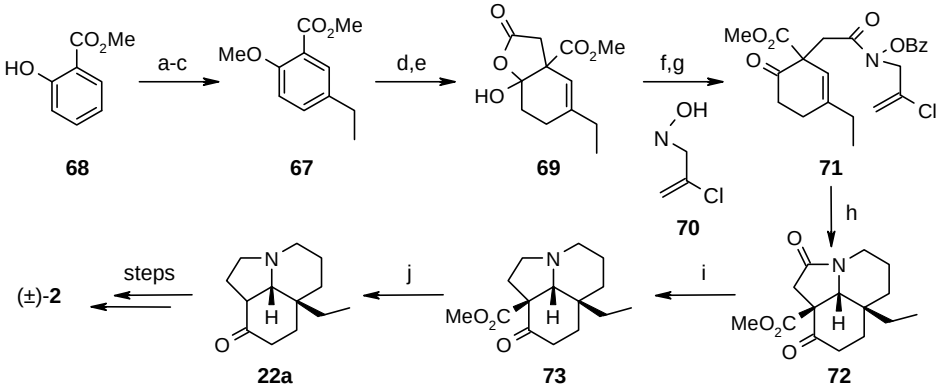
In 2006 Zard *et al*. reported an approach to aspidospermidine **2** using a cascade reaction of amidyl radical **66** to construct the CDE tricycle **65** (Scheme 13).[19]



Scheme 13: Retrosynthetic strategy employed by Zard *et al*.[19]

Their precursor for the amidyl radical cyclisation was synthesized according to Scheme 14. Thus, a Birch reduction of **67** with $BrCH_2CO_2t$-Bu quench yielded lactone **69** on treatment with aq. HCl, a precursor of **71**. Treating **71** under radical forming conditions initiated the desired 5-*exo*/6-*endo* sequential cyclisation to give tricycle **72** in 53% yield together with 23% of the mono-cyclisation product. 6-*endo* Cyclisation was promoted in the second ring closure by incorporation of a chlorine atom on the alkene acceptor. The tricycle **72** was then transformed to the aminoketone **22a** by selective reduction of the lactam with 9-BBN and decarboxylation of the β-keto ester with LiCl in DMF (Scheme 14).

Zard's synthesis achieves the synthesis of the late stage aminoketone **22a** in 19.8% overall yield in 10 steps. The tricycle (**22a**) was then converted to aspidospermidine **2** by the Fischer-indole cyclisation protocol.

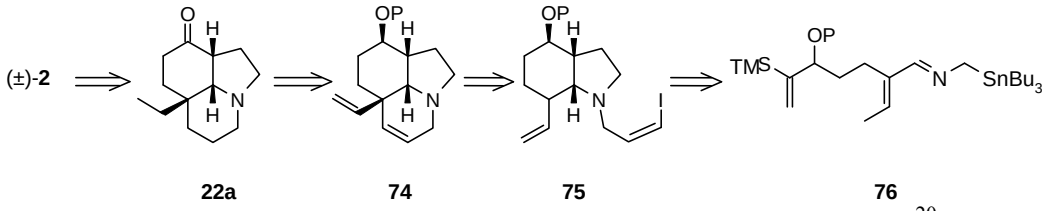


Scheme 14: Zard's synthesis of (±)-aspidospermidine **2**.[19]

Reagents and conditions: (a) $AlCl_3$, AcCl, CH_2Cl_2, 98%; (b) H_2, Pd(0), MeOH, 91%; (c) MeI, K_2CO_3, acetone, 85%; (d) Li, NH_3, *t*-BuOH, THF, $BrCH_2CO_2t$-Bu; (e) HCl (aq.), THF, 90% (2 steps); (f) (1) isobutylchloroformate, Et_3N, (2) hydroxylamine **70**; (g) BzCl, Et_3N, CH_2Cl_2, 67% (2 steps); (h) Bu_3SnH, VAZO, α,α,α-trifluorotoluene, 53%; (i) 9-BBN, THF, Δ, 93%; (j) LiCl, DMF, 140 °C, 88%.

Pearson's [3+2] cycloaddition approach.

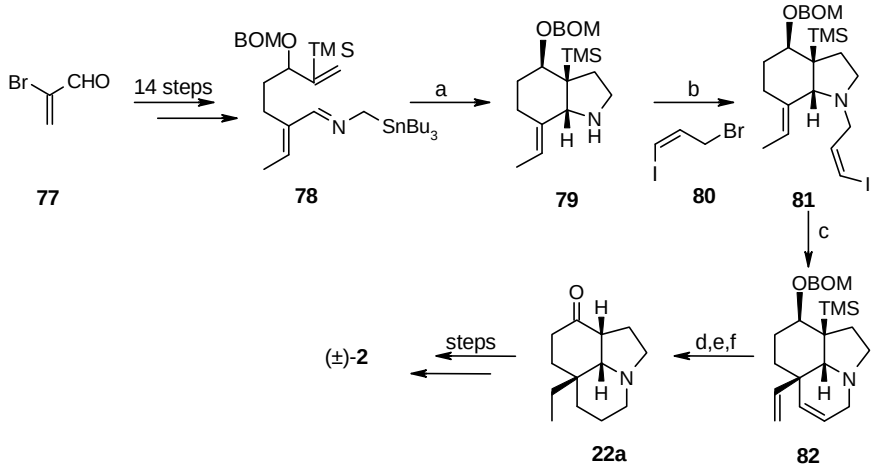
Also in 2006, Pearson *et al*. reported their formal total synthesis of three *Aspidosperma* alkaloids, including aspidospermidine **2**, through the preparation of Stork's intermediate **22**.[20] Key steps in their sequence were a *n*-BuLi induced [3+2] cycloaddition of **76** to install rings C and E and an intramolecular Heck cyclisation of vinyl iodide **75** to install ring D (Scheme 15).



22a **74** **75** **76**

Scheme 15: Retrosynthetic strategy employed by Pearson *et al*.[20]

The key intermediate **76** was synthesized in a 14 step chain extension sequence from 2-bromoacrolein **77**. Treatment of imine **78** with a dilute solution of *n*-BuLi gave cycloadduct **79** following successful [3+2] cycloaddition. *N*-alkylation of **79** with the allyl bromide **80** incorporates the vinyl iodide to give **81** which, under Heck conditions, gave tricyclic amine **82**. A 2 step procedure was necessary to reduce the diene moieties and remove the BOM protecting group. Oxidation of the resultant alcohol with Dess-Martin then gave aminoketone **22a** to complete the formal total synthesis (Scheme 16).



77 **78** **79** **80** **81** **82** **22a**

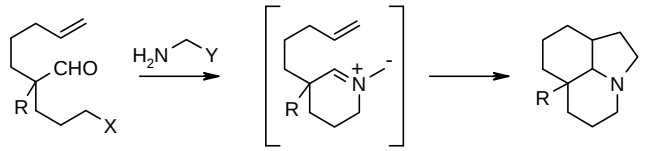
Scheme 16: Pearson's formal synthesis of (±)-aspidospermidine A**2**.[20]

Reagents and conditions: (a) BuLi (2 equiv.), THF, −78 °C, then H_2O; (b) **80**, THF, K_2CO_3, 59% (2 steps); (c) $Pd(OAc)_2$, K_2CO_3, Bu_4NCl, DMF, 43%; (d) H_2, 10% Pd/C, MeOH, TFA, 98%; (e) Li, THF/NH_3, NH_4Cl, HCl, H_2O/MeOH/THF; (f) Dess-Martin, HCl, H_2O/Et_2O, 54% (2 steps).

Pearson achieved the synthesis of aminoketone **22a** in 20 steps from 2-bromoacrolein **77** in 4.6% overall yield. A lengthy synthesis gave access to the key intermediate **78** and the closing steps are let down by the low yielding Heck reaction and dissolving metal reduction/oxidation sequence.

Coldham's cyclisation/cycloadditon cascade approach to tricyclic amines.

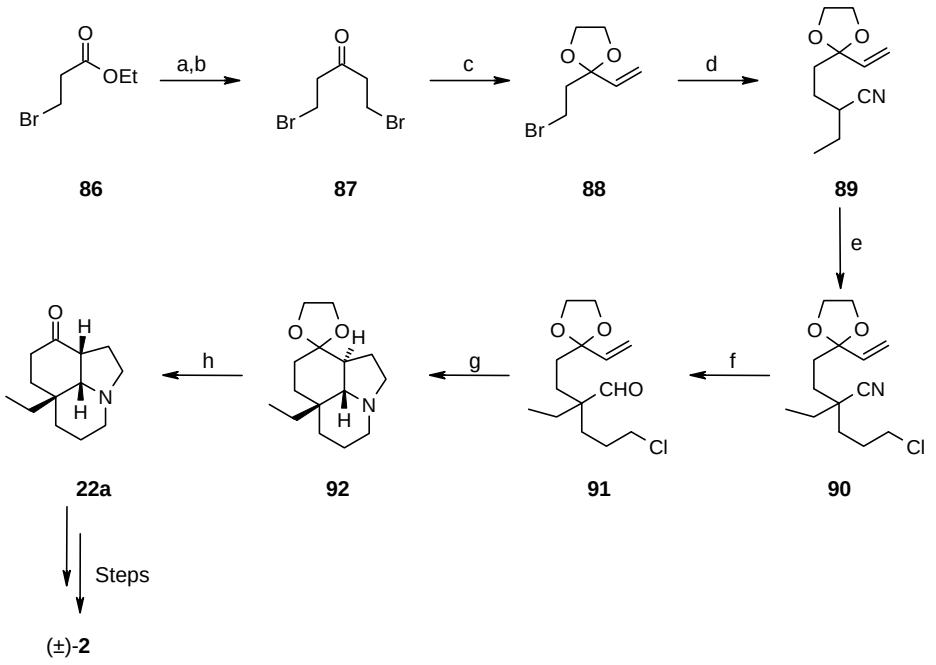
The most recent total synthesis of aspidospermidine **2** was accomplished by Coldham *et al*.[21] In a variation of Pearson's [3+2] cycloaddition approach,[20] Coldham envisioned a cyclisation/cycloaddition strategy to access tricyclic amine **85** in one pot from acyclic precursors (Scheme 17). Coldham believed it should be possible to form the ylide from an aldehyde and amine together with *in situ N*-alkylation and loss of Y by desilylation, destannylation or decarboxylation.



83 **84** **85**

Scheme 17: Coldham *et al*.'s planned synthesis of tricyclic amines (X = leaving group and Y = $SiMe_3$, $SnBu_3$ or CO_2H).[21]

Known di-bromoketone **87** was readily prepared from ethyl 3-bromopropionate **86** and subsequently transformed to protected enone **88**. Sequential alkylation reactions then installed the nitrile functionality and side chain to give **90**. Reduction of the nitrile with DIBAL-H provided the key aldehyde **91**. Treatment of **91** with glycine in the presence of 10 mol% camphorsulfonic acid initiated successful cyclisation/cycloaddition to tricyclic amine **92**. Hydrolysis of the ketal with aq. acid along with isomerisation of the adjacent stereocentre provided the aminoketone **22a**. The previously reported 3 step procedure of Stork *et al*. was then employed to complete the total synthesis of (±)-**2** (Scheme 18).



Scheme 18: Coldham's total synthesis of (±)-aspidospermidine **2**.[21]

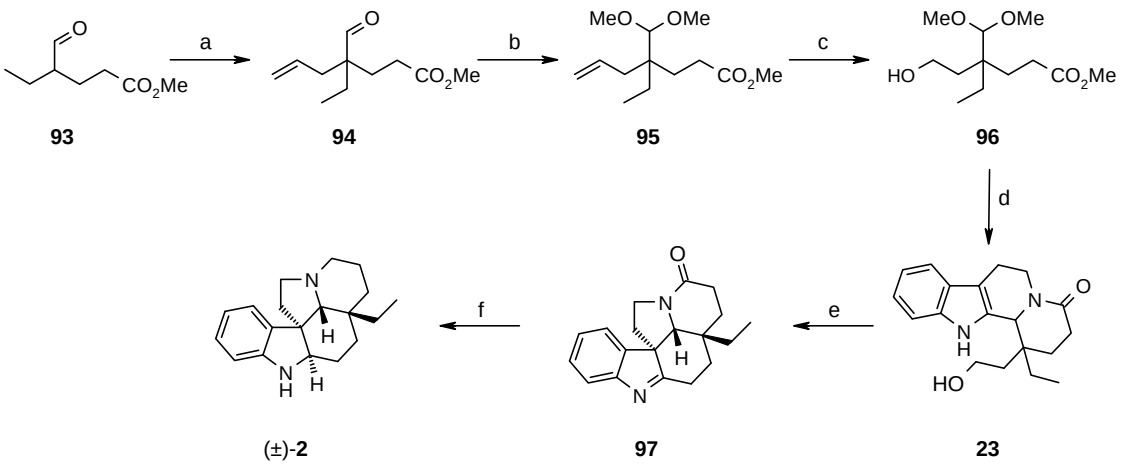
Reagents and conditions: (a) EtMgBr (2.2 equiv.), Ti(O*i*-Pr)$_4$ (0.1 equiv.), Et_2O; (b) NBS, CCl_4, 82% (2 steps); (c) $HOCH_2CH_2OH$, benzene, *p*-TsOH, Δ, 18 h, then *t*-BuOK, THF/toluene, 0 °C, 2 h, 82%; (d) $EtCH_2CN$, LDA, THF, −78 °C, then **88**, 88%; (e) LDA, THF, −78 °C, 1 h, then 1-bromo-3-chloropropane, 96%; (f) DIBAL-H, CH_2Cl_2, −78 °C, then oxalic acid (0.5 M), 82%; (g) $H_2NCH_2CO_2H$, toluene, camphorsulfonic acid (10 mol%), Δ, 18 h, 79%; (h) 5% aq. HCl/THF, 80 °C, 1 h, 89%.

Coldham's synthesis exploits a cascade sequence to prepare the tricyclic amine **92** from **91**, forming four new σ-bonds, three rings and three new stereocentres in the "one pot". The route provides rapid access to Stork's late stage intermediate in 8 steps from **86** in 32.8% overall yield.

Strategy B – Harley-Mason's rearrangement/cyclisation approach to the *Aspidosperma* skeleton.

In 1967 Harley-Mason *et al*. reported an elegant synthesis of (±)-aspidospermidine **2** wherein the CDE rings were appended onto tryptamine using the acyclic precursor **96**.[13] Alkylation of the pyrrolidine enamine of methyl 4-formylhexanoate **93** with allyl bromide afforded aldehyde **94**, which was subsequently converted to dimethyl acetal **95**. Reductive ozonolysis of the terminal alkene afforded alcohol **96** which reacted smoothly with tryptamine to give hydroxy-

lactam **23**. Treatment of **23** with refluxing sulfuric acid induced cyclisation to C2 of the indole and rearrangement to the *Aspidosperma* skeleton, giving **97**. $LiAlH_4$ reduction completed the total synthesis of (±)-aspidospermidine **2** in 20-25% yield from tryptamine (Scheme 19).



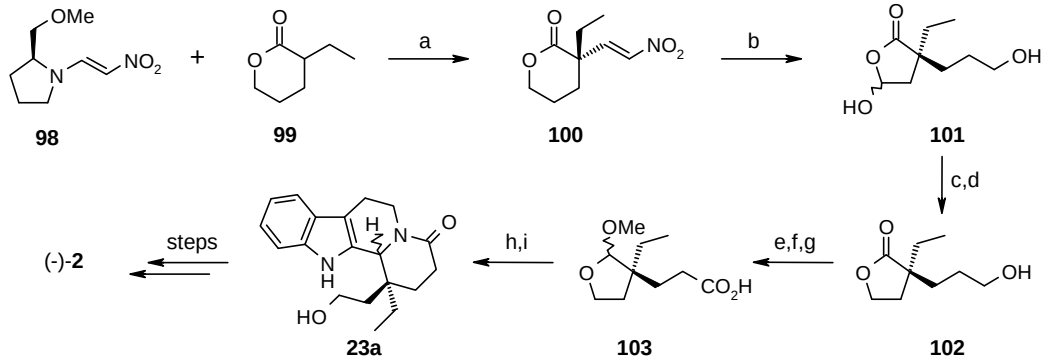
Scheme 19: Harley-Mason's total synthesis of (±)-aspidospermidine **2**.[13]

Reagents and conditions: (a) Pyrrolidine, allyl bromide; (b) trimethyl orthoformate; (c) O_3 then $NaBH_4$; (d) tryptamine, AcOH, Δ; (e) 40% H_2SO_4 (or $BF_3.Et_2O$), 100 °C; (f) $LiAlH_4$.

Asymmetric approaches to aspidospermidine using the Harley-Mason methodology.

A number of asymmetric total syntheses of aspidospermidine have been reported using the cyclisation-rearrangement approach introduced by Harley-Mason and co-workers.[13] All involve the development of routes to cyclic analogues of **96** with the absolute stereochemistry at the quaternary centre set. Fuji[22] and Schultz[23] independently targeted (−)-aspidospermidine, the unnatural enantiomer of the natural product, while Okada[24] pursued (+)-aspidospermidine.

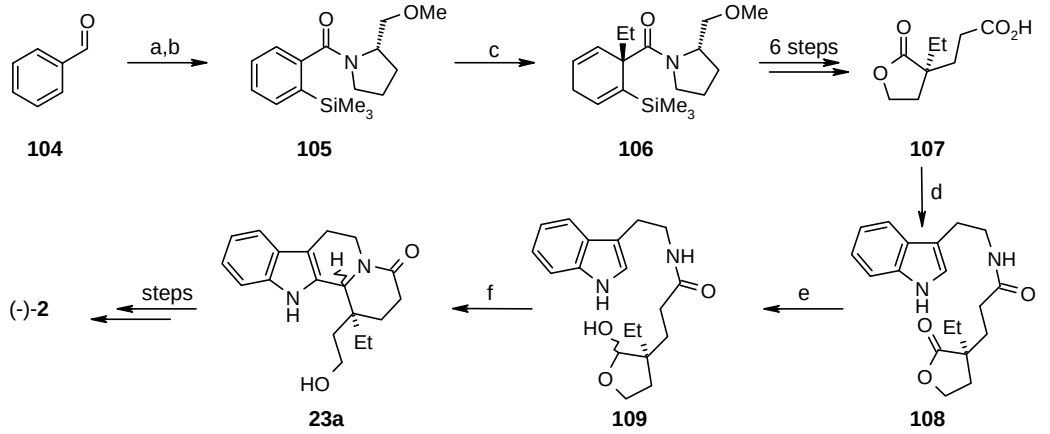
Fuji and coworkers prepared hydroxy lactam **23a** as a 1:1 mixture of isomers in 9 steps from **98** in 47.7% overall yield.[22] The Harley-Mason cyclisation-rearrangement strategy[13] followed by reduction then gave (−)-aspidospermidine **2** (Scheme 20). This short efficient synthesis used the conjugate addition of the ester enolate of **99** to **98** to install the stereogenic centre. Reductive denitration of **100** then gave hemiacetal **101**. Reduction to chiral lactone alcohol **102** and conversion to acetal **103** facilitated condensation with tryptamine to the desired intermediate **23a**.



Scheme 20: Fuji's total synthesis of (−)-aspidospermidine **2**.[22]

Reagents and conditions: (a) BuLi, DME/Et_2O, −78 °C, 99%; (b) $TiCl_3$, DME, pH 5; (c) $NaBH_4$; (d) HCl, MeOH, Δ, 75% (3 steps); (e) CrO_3, H_2SO_4, acetone; (f) DIBAL-H, Et_2O; (g) TsOH, MeOH, Δ, 76% (3 steps); (h) tryptamine, AcOH, Δ; (i) NaOH, MeOH, 84%, (2 steps).

Schultz *et al*.[23] reported a synthesis of enantiomerically pure **107**, a cyclic analogue of Harley-Mason's intermediate **96**. The key step in its preparation involved a diastereoselective dissolving metal reduction-alkylation sequence, which set the C5 quaternary carbon centre giving **106**. A six step procedure afforded lactone **107** which underwent condensation with tryptamine to **108**. DIBAL-H reduction to lactol **109**, and acetic acid-induced cyclisation gave hydroxy lactam **23a** as a 1:1 mixture of diastereoisomers, completing a formal total synthesis (Scheme 21).

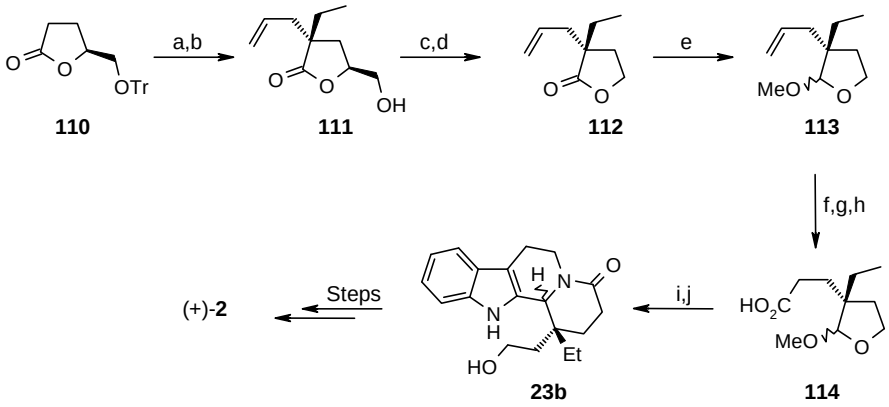


Scheme 21: Schultz's total synthesis of (−)-aspidospermidine **2**.[23]

Reagents and conditions: (a) $MeHN(CH_2)_2NMe_2$, *n*-BuLi, TMSCl, −20 °C, 24 h, then H_3O^+, 87%; (b) (1) $KMnO_4$, acetone, H_2O, 94%; (2) $(COCl)_2$, CH_2Cl_2, DMF, RT, 5 h, *S*-prolinol, CH_2Cl_2, -40 °C then Et_3N; (3) NaH, THF, 0 °C, MeI, Δ, 5 h, 88% (2 steps); (c) K, NH_3, *t*-BuOH, THF, −78 °C, LiBr, piperylene, EtI, −78 °C, 97%; (d) tryptamine, $(PhO)_2P(O)N_3$, Et_3N, THF, 84%; (e) DIBAL-H, CH_2Cl_2, −78 °C, 93%; (f) AcOH, Δ, 20% NaOH/MeOH, 65 %.

The asymmetric synthesis was completed using the Harley-Mason rearrangement procedure to give (−)-aspidospermidine **2**. Schultz's synthetic route is the longest of this group with 18 linear steps to **2** in 13.6% yield.

More recently Okada *et al*. reported an asymmetric synthesis of (+)-aspidospermidine via hydroxy lactam **23b**.[24] This short synthesis introduced the key stereogenic centre by sequential alkylation of (*S*)-γ-trityloxymethyl-γ-butyrolactone **110**, firstly with ethyl iodide and then allyl bromide to give, after detritylation, **111**. Complete removal of the hydroxy-bearing side chain provided **112** which, following reduction of the lactone and protection of the resultant lactol gave methyl acetal **113**. Manipulation of the alkene side chain led to acid **114** which was condensed with tryptamine to give hydroxy-lactam **23b** as a 1:1 mixture of diastereoisomers (Scheme 22).



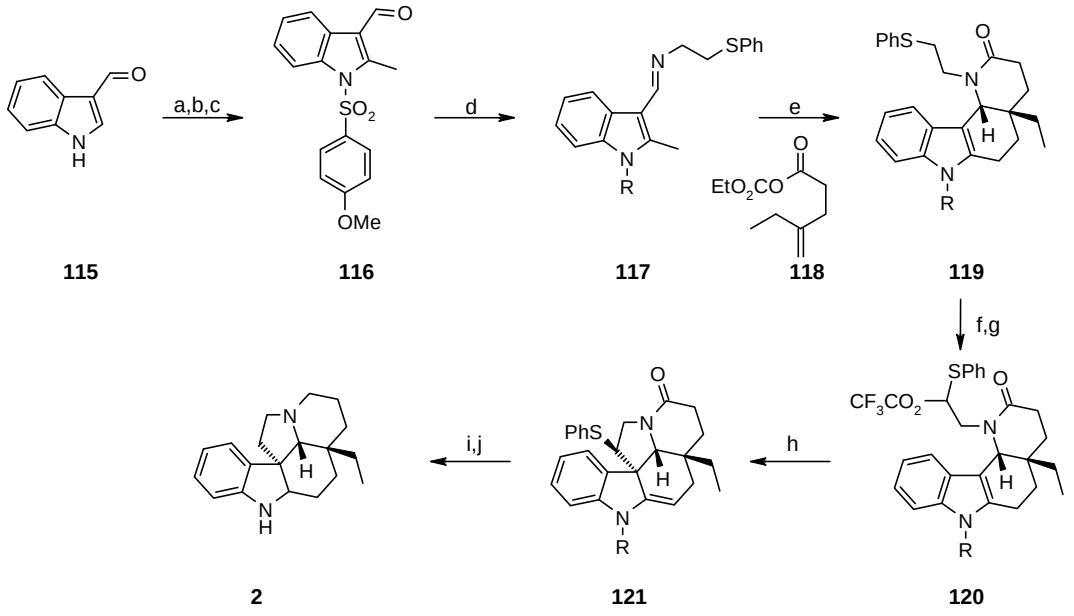
Scheme 22: Okada's total synthesis of (+)-aspidospermidine **2**.[24]

Reagents and conditions: (a) LDA, HMPA, EtI then, LDA, HMPA, allyl bromide, THF, −78 °C, 93%; (b) 80% AcOH, 80 °C, 1 h, 98%; (c) 4 M aq. NaOH, dioxane, 100 °C, 1 h, CO_2, aq. $NaIO_4$, RT, 3 h, 1 M HCl, 95%; (d) $NaBH_4$, MeOH, RT, 1 h then, 4 M HCl-MeOH, 70 °C, 1 h, 92%; (e) DIBAL-H, Et_2O, −78 °C, 1 h then, $CH(OMe)_3$, *p*-TsOH, MeOH, 80 °C, 40 min, 84%; (f) 9-BBN, THF, RT, 16 h then, 30% H_2O_2, 3 M aq. NaOH, THF, RT, 1 h, 87%; (g) SO_3-Py, DMSO, NEt_3, CH_2Cl_2, RT, 0.5 h; (h) $NaClO_2$, *t*-BuOH, aq. NaH_2PO_4, Me_2C=CHMe, RT, 1 h, 95% (2 steps); (i) tryptamine, AcOH, 125 °C, 6 days, 87%; (j) 20% aq. NaOH, MeOH, RT, 1 h, 72%.

Okada's route gave hydroxy lactam **23b** in 10 steps and 34.6% overall yield, allowing an asymmetric route of (+)-aspidospermidine to be completed.

Strategy C–Magnus' end game E-ring closure.

The final group employ similar end game methodologies to that developed by Magnus *et al*. to close ring E.[25] Magnus built the ABCD ring system through cyclisation of imine **117** with anhydride **118** to give **119** (Scheme 23). This tetracycle was then converted into pentacycle **121** through an intramolecular Pummerer reaction, closing ring E. Desulfurisation with Raney nickel and subsequent $LiAlH_4$ reduction afforded (±)-aspidospermidine **2**. This short synthesis (10 steps) achieved the natural product target in 3.4% overall yield from indole 3-carboxaldehyde **115**. The approach is let down by a low yielding step to install the requisite methyl at C2 of the indole centre in **116**. The low yield associated with formation of tetracycle **119** (33%) from **117** and **118** is balanced by the formation of 2 new rings and 3 key bonds in the one step. The Pummerer rearrangement strategy to close ring E, giving **121**, is accomplished in 79% yield from **119** in 3 steps.



Scheme 23: Magnus' total synthesis of (±)-aspidospermidine **2**.[25]

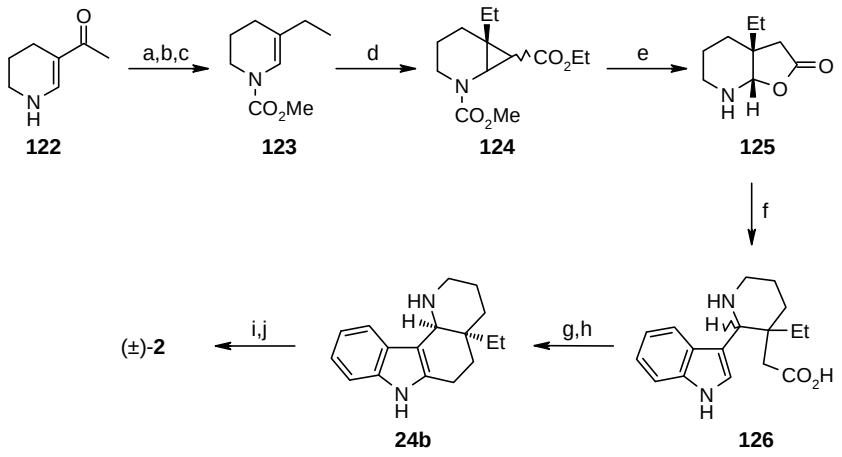
Reagents and conditions: (a) NaH, glyme, imidazole, 4-methoxybenzenesulfonyl chloride, Δ, 2 h, 70%; (b) *t*-$BuNH_2$, CH_2Cl_2; (c) BuLi, THF, MeI, −78 °C to RT, 16 h, 43% (2 steps); (d) 2-(phenylthio)ethylamine, 100%; (e) **118**, chlorobenzene, 140 °C, 2.75 h, 33%; (f) MCPBA, CH_2Cl_2, $NaHCO_3$, 0 °C, 97%; (g) Trifluoroacetic anhydride, CH_2Cl_2, 0 °C, 10 min; (h) chlorobenzene, 130 °C, 2.5 h, 81% (2 steps); (i) Raney nickel, EtOH, 20 °C, 1 h, 81%; (j) $LiAlH_4$, THF, 20 °C, 48 h, 54%.

Numerous groups have reported synthesis of aspidospermidine using the E ring closing strategy of Magnus *et al*. These syntheses, six in total, employ

independent methods to establish the required ABCD ring system and are split into those which condense onto a ready formed indole nucleus and those which form the indole (AB) ring as a late stage development.

E Ring closing strategy, routes to ABCD system via indole condensation.

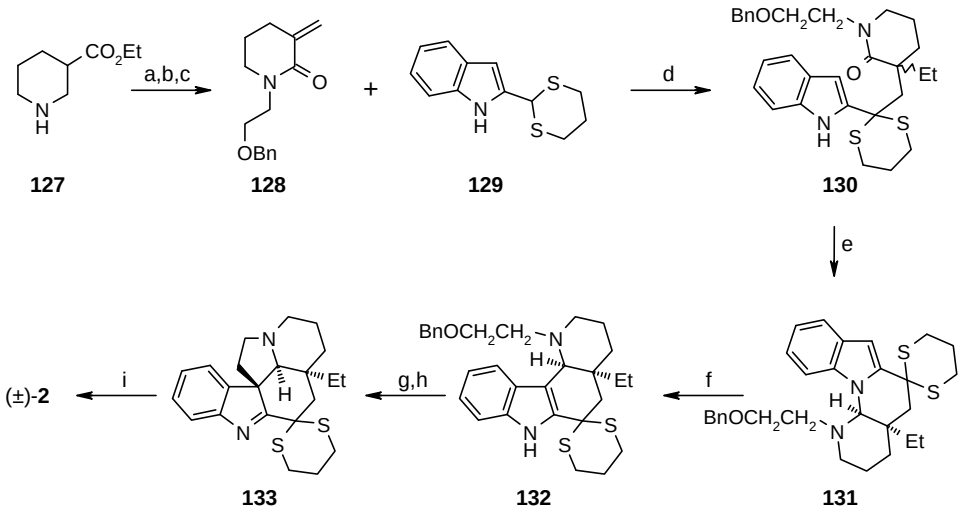
Wenkert's 1988 synthesis of (±)-aspidospermidine **2**[26] accomplished the target according to Scheme 24. Carbinolamine lactone **125** was prepared by alkaline hydrolysis of cyclopropanecarboxylate **124**, itself formed from enamide **123**. The lactone was then condensed with indole in acetic acid to give amino acid **126**. Cyclisation promoted by PPA installed the C ring giving **24b** after $LiAlH_4$ reduction. E ring closure was then accomplished by heating **24b** in the presence of 1,2-dibromoethane to install the remaining 2 carbons of the *Aspidosperma* skeleton. $LiAlH_4$ reduction completes the sequence giving the natural product (±)-**2** in 10 linear steps from **122** and 4.0% overall yield. The closing of ring E was accomplished in only 32% yield to achieve the pentacycle (±)-**2**.



Scheme 24: Wenkert's total synthesis of (±)-aspidospermidine **2**.[26]

Reagents and conditions: (a) Methyl chlorocarbonate, NEt_3, THF, 0 °C, 4 h, then HCl, 91%; (b) HBr, Et_2O, 0 °C, 10 min, 1,3-propanedithiol, RT, 4 h, 48%; (c) W-2 Raney nickel, EtOH, Δ, 12 h, 93%; (d) Ethyl diazoacetate, copper bronze, 135 °C, 0.5 h, 95%; (e) KOH, H_2O, diethylene glycol, 110 °C, 12 h, then HCl to pH 7, 88%; (f) indole, dioxane, HCl, 10% aq. AcOH, 80 °C, 18 h, 89%; (g) PPA, 90 °C, 45 min, 61%; (h) $LiAlH_4$, dioxane, Δ, 18 h, 97%; (i) K_2CO_3, 1,2-dibromoethane, 140 °C, 20 min, 32%; (j) $LiAlH_4$, Et_2O, RT, 2 h, 70%.

Rubiralta *et al*.[27] set up the ABCD ring system through a tandem Michael addition-cyclisation of dithiane **129** with 3-methylene lactam **128** and ethyl iodide. Partial reduction of the resultant lactam **130** with DIBAL-H induced spontaneous cyclisation to **131** which, when treated with acetic acid, isomerizes to give the ABCD ring system **132**. Finally, debenzylation, closure of ring E (*via* the tosylate) and reduction of the dithiane gave aspidospermidine **2** in 9 steps from **127** and 11% overall yield. E ring closure proved much more efficient *via* base mediated displacement of a tosylate, with this achieved in 77% from the corresponding alcohol (Scheme 25).



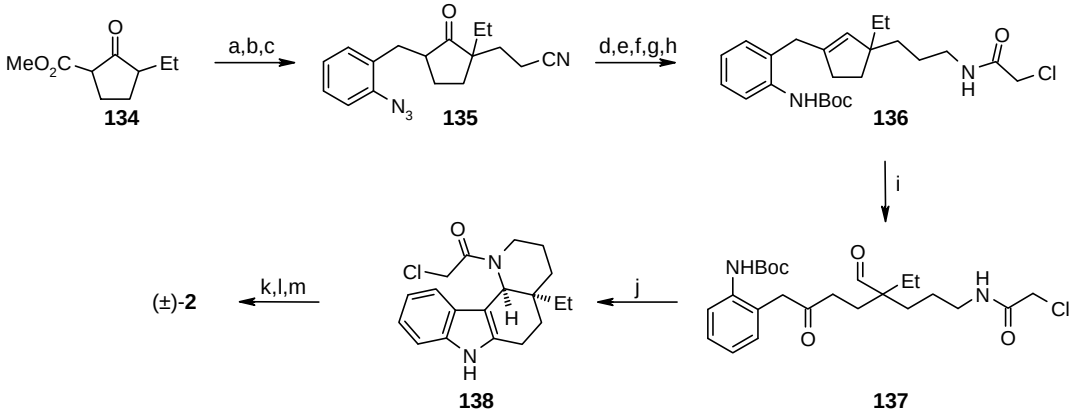
Scheme 25: Rubiralta's total synthesis of (±)-aspidospermidine **2**.[27]

Reagents and conditions: (a) K_2CO_3, PhH, bromoethyl benzyl ether, Δ, 24 h, 89%; (b) 6 M HCl, RT, 12 h, 100%; (c) Ac_2O, Δ, 4 h, then aq. K_2CO_3, 0 °C, 4 h, 86%; (d) *n*-BuLi, THF, HMPA, EtI, −78 °C, 2 h, 52%; (e) DIBAL-H, THF, 0 °C, 73%; (f) 50% aq. AcOH, Δ, 2 h, 90%; (g) Me_2S, CH_2Cl_2, $BF_3.Et_2O$, 35 °C, 2 h, 86%; (h) *t*-BuOK, TsCl, THF, 1 h, RT, 77%; (i) W-2 Raney nickel, dioxane, Δ, 30 min, 65%.

E Ring closing strategy, routes to ABCD system via indole formation.

Heathcock[28] established the ABCD ring system from acyclic precursor **137** using a pivotal intramolecular cascade to simultaneously form rings B, C and D (Scheme 26). A nine step sequence established precursor **137**, which on treatment with TFA in dichloromethane initiates Boc deprotection, imine formation and two cyclisation reactions to give **138**. Ring E was installed by conversion of the

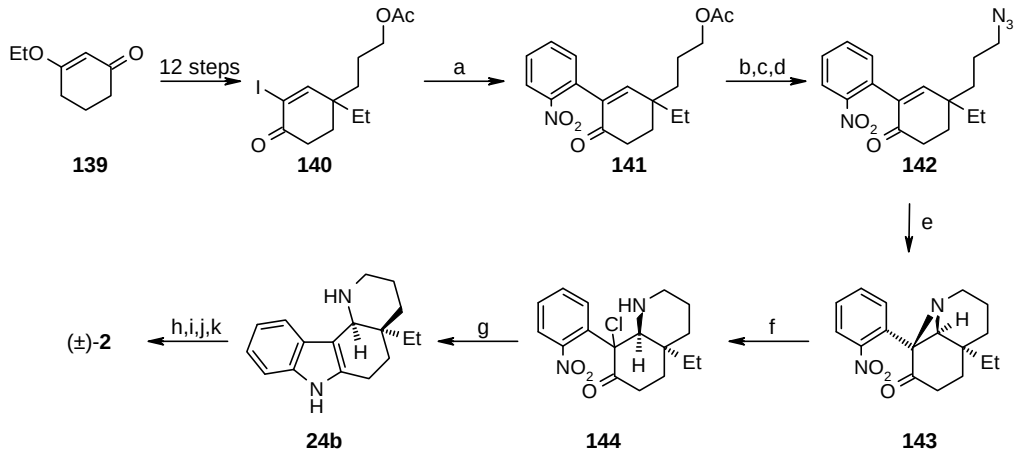
chloroacetate **138** to the more reactive iodoacetate which, when treated with silver triflate, underwent cyclisation in 86%. Reduction of the lactam carbonyl completed the total synthesis of (±)-**2**. Heathcock accomplished the target in 13 linear steps in 4.9% overall yield from **134**.[28]



Scheme 26: Heathcock's total synthesis of (±)-aspidospermidine **2**.[28]

Reagents and conditions: (a) *o*-azidobenzyl bromide, Cs_2CO_3, acetone, 94%; (b) acrylonitrile, Cs_2CO_3, *t*-BuOH; (c) KOH, 77% (2 steps); (d) $CeCl_3.7H_2O$, $NaBH_4$, MeOH; (e) PCl_5, pyridine, 63% (2 steps); (f) $LiAlH_4$, 65%; (g) $(ClCH_2CO)_2O$, NEt_3; (h) Boc_2O, NEt_3, 63% (2 steps); (i) O_3, −78 °C, then Me_2S; (j) 1:1 TFA: CH_2Cl_2, 37% (2 steps); (k) NaI, acetone; (l) CF_3SO_3Ag, 86%; (m) $LiAlH_4$, 82%.

Banwell[29] used a Pd[0]-catalysed Ullmann cross-coupling of iodide **140** (prepared in 12 steps from commercially available 3-ethoxycyclohexenone **139**) and *o*-iodonitrobenzene. The coupling was achieved in 75% affording the acetate **141**, which was transformed into azide **142**. Heating azide **142** in benzene for 3 days afforded aziridine **143** in good yield (72%) (Scheme 27).



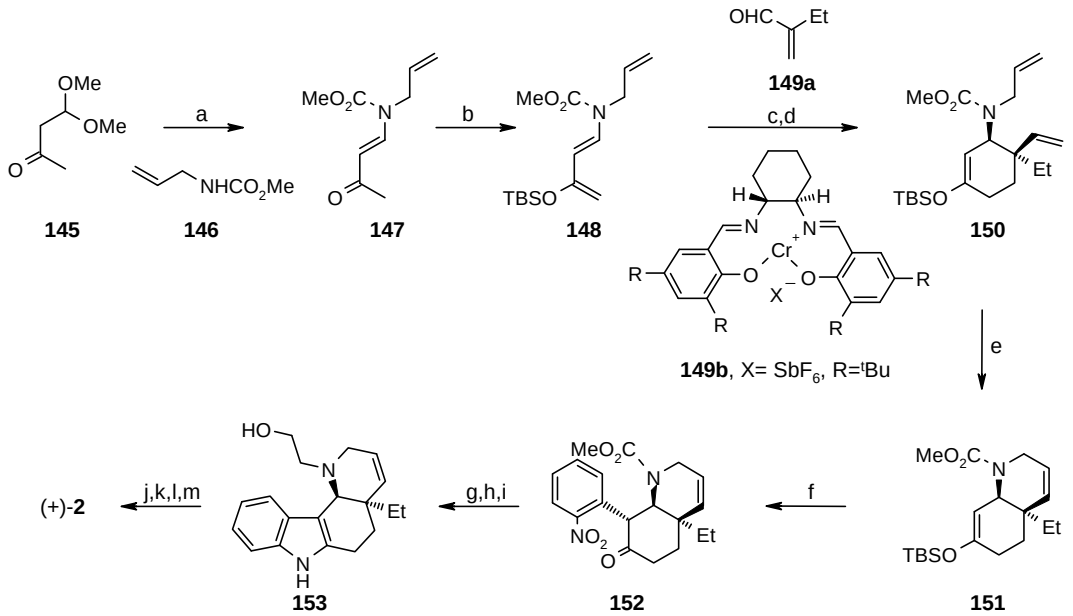
139 **140** **141** **142** **143** **144** **24b**

Scheme 27: Banwell's total synthesis of (±)-aspidospermidine **2**.[29]

Reagents and conditions: (a) *o*-nitroiodobenzene (2 equiv.), Cu, $Pd_2(dba)_3$ (cat), DMSO, 70 °C, 5 h, 75%; (b) aq. K_2CO_3, MeOH, 18 °C, 16 h; (c) MsCl, NEt_3, Et_2O, 0 to 18 °C, 2 h; (d) NaN_3 (3 equiv.), DMF, 67 °C, 3 h, 87% (3 steps); (e) PhH, 75 °C, 3 d, 72%; (f) 1 M HCl in Et_2O, CH_2Cl_2, −15 °C, 1.5 h; (g) $TiCl_3$.3THF (10 equiv.), H_2O, 2.5 M aq. NH_4OAc, acetone, 18 °C, 20 min, 46% (2 steps); (h) α-chloroacetyl chloride, NEt_3, CH_2Cl_2, 0 to 18 °C, 2 h, 69%; (i) NaI (10 equiv.), acetone, 56 °C, 2 h; (j) AgOTf (2 equiv.), THF, 18 °C, 30 min; (k) $LiAlH_4$, THF, 66 °C, 2 h, 47% (3 steps).

Regioselective cleavage to **144** and reduction to indole **24b** allowed Heathcock's E ring closing procedure to be mirrored to complete a total synthesis of (±)-aspidospermidine **2**. Banwell's lengthy synthesis, 23 steps, achieves the target in 1.8% overall yield.

The remaining syntheses in this group lead to asymmetric syntheses of (+)-aspidospermidine. D'Angelo's approach[30] employs a condensation between 2-iodoaniline and dione **156** to establish the indole portion of the system and ABC rings onto which rings D and E are incorporated. Rawal's synthesis[31] similarly builds up the ring system sequentially but establishes the indole moiety *via* the ACD ring system akin to the Banwell approach.

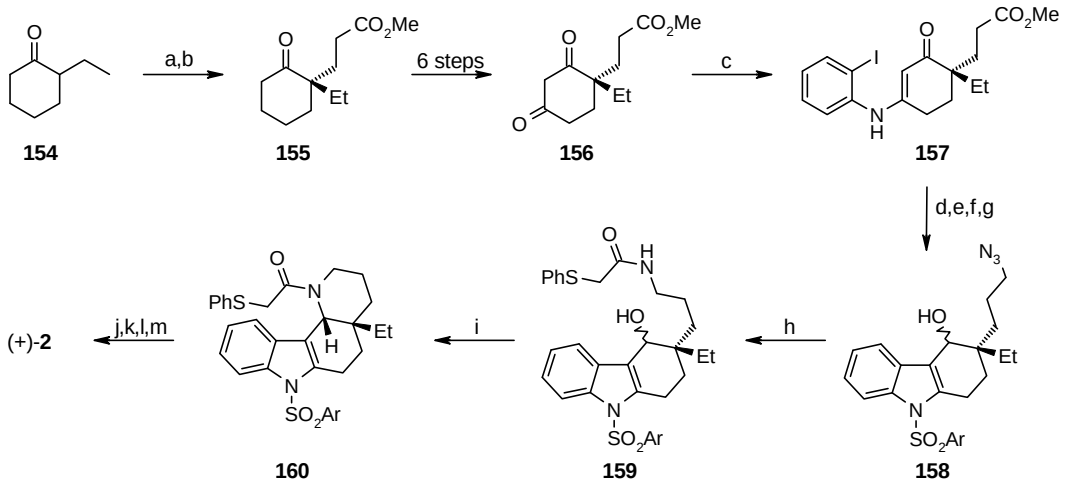


Scheme 28: Rawal's total synthesis of (+)-aspidospermidine **2**.[31]

Reagents and conditions: (a) **146**, TsOH (cat.), $CHCl_3$, Δ, 1-2 d, 90%; (b) NaHMDS, TBSCl, −78 °C, THF, 100%; (c) **149a**, 5 mol% **149b**, CH_2Cl_2, −40 °C, 2 d, 91%; (d) Ph_3PCH_3Br, *n*-BuLi, THF, −78 °C, 85%; (e) PhH, Schrock's molybdenum catalyst (5 mol%), 60 °C, 1 h, 88%; (f) NPIF, DMSO, THF, 94%; (g) $TiCl_3$, NH_4OAc, THF, H_2O, 89%; (h) TMSI (2 equiv.), CH_2Cl_2, MeOH, Δ, 90%; (i) $BrCH_2CH_2OH$ (10 equiv.), Na_2CO_3, EtOH, Δ, 18 h, 100%; (j) MsCl, NEt_3, CH_2Cl_2, 90%; (k) *t*-BuOK, THF, 87%; (l) $NaBH_4$, EtOH; (m) H_2, PtO_2, EtOH, 73% (2 steps).

Rawal's synthesis[31] employed an enantioselective Diels-Alder reaction between 1-amino-3-siloxydiene **148** and ethylacrolein **149** to introduce the C5 stereogenic centre. Converting the resultant aldehyde to triene **150** allowed ring D to be installed by ring-closing metathesis to give bicycle **151**. (*o*-Nitrophenyl)phenyliodonium fluoride (NPIF) was next used to introduce an *o*-nitrophenyl group, giving **152**. Reduction of the nitro group, indole formation and *N*-alkylation then yielded **153**. E ring closure was achieved in a similar fashion to Rubiralta, through mesylation and base-induced cyclisation. Finally, imine reduction ($NaBH_4$) and hydrogenation of the remaining olefin completed the total synthesis of (+)-aspidospermidine **2.** Rawal's asymmetric synthesis was completed in relatively few steps (13) in 28% overall yield (Scheme 28).

Earlier, d'Angelo had completed an asymmetric synthesis of (+)-**2**[30] using an asymmetric Michael addition a chiral enamine derived from **154** to introduce the C5 stereogenic centre. The resulting cyclohexanone **155** was transformed into the cyclohexane-1,3-dione **156** in 6 steps and 35% yield, which was then condensed with 2-iodoaniline to give precursor **157** (Scheme 29). Cyclisation and elaboration to amide **159** set up a TFA induced cyclisation to give tetracycle **160** as a single isomer. E ring closure mirrored that of Magnus *et al*.[25] Removal of the residual sulfur functionality and $LiAlH_4$ reduction of the amide completed the asymmetric synthesis of the target in 22 steps from **154** in 2.7% overall yield.

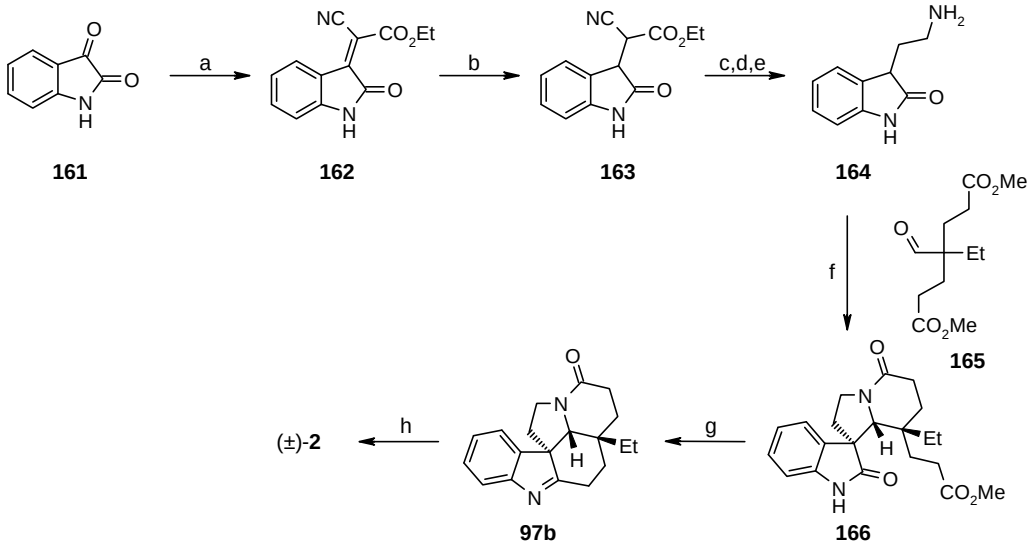


Scheme 29: D'Angelo's total synthesis of (+)-aspidospermidine **2**.[30]

Reagents and conditions: (a) (*R*)-(+)-phenylethylamine, toluene, *p*-TsOH, Dean-Stark, Δ, 12 h; (b) methyl acrylate, hydroquinone, 65 °C, 3 d, then AcOH, THF, RT, 3 h, 83%; (c) 2-iodoaniline, *p*-TsOH, toluene, Dean-Stark, Δ, 5 h, 94%; (d) NaH, HMPA, CuI, 120 °C, 2 h, 84%; (e) $LiEt_3BH$, THF, −40 °C, 1 h, then EtOH, 6 N NaOH, 0 °C, then 30% H_2O_2, RT, 15 h, 88%; (f) (1) NEt_3, DMAP, CH_2Cl_2, THF, MsCl, 2 h, (2) DMF, NaN_3, 80 °C, 2 h, (3) tetrabutylammonium hydrogensulfate, (*p*-methoxyphenyl)sulfonyl chloride, CH_2Cl_2, 50 % aq. NaOH, 2 h, RT, 74%; (g) $NaBH_4$, EtOH, Δ, 30 min, 92%; (h) PPh_3, THF, 18 h, H_2O, RT, 12 h, CH_2Cl_2, 0 °C, (phenylthio)acetyl chloride, NaOH, 30 min, 62%; (i) TFA, CH_2Cl_2, 0 °C, 15 min, 94%; (j) sodium *m*-periodate, THF, MeOH, H_2O, RT, 72 h, 88%; (k) trifluoroacetic anhydride, CH_2Cl_2, 0 °C, 15 min, chlorobenzene, 135 °C, 2 h, 89%; (l) W-2 Raney nickel, EtOH, DMF, 20 min, RT, 56%; (m) $LiAlH_4$, THF, 0 °C, RT, 48 h, 68%.

Other syntheses.

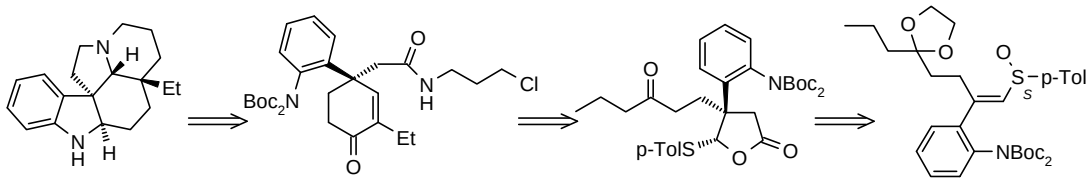
Four further approaches are worthy of note here. Laronze and Levy reported a short total synthesis of aspidospermidine in 1974 (Scheme 30),[32] wherein the 2-hydroxytryptamine equivalent **164** was prepared in a five step process from isatin **161** according to the procedure reported by Harley-Mason.[33] This was then condensed with tricarbonyl diester **165** (prepared by exhaustive alkylation of butraldehyde) to give tetracycle **166** which, on treatment with PPA, underwent cyclisation, hydrolysis and decarboxylation to give **97b**. $LiAlH_4$ reduction of the lactam and imine gave the target pentacycle (±)-**2** in 8 steps from isatin in 7.3% overall yield.



Scheme 30: Laronze and Levy's total synthesis of (±)-aspidospermidine **2**.[32]

Reagents and conditions: (a) Ethyl cyanoacetate, EtOH, piperidine, Δ, 4 h, 73%; (b) 3 N HCl, zinc dust, EtOAc, 90%; (c) 10% aq. NaOH, Δ, 4 min, then HCl, 84%; (d) ethylene glycol monoethyl ether, Δ, 2 h, 75%; (e) H_2, PtO_2, HCl, EtOH, H_2O, RT, 60%; (f) **165**, benzene, Δ, 62%; (g) PPA, 125 °C, 10 h, 68%; (h) $LiAlH_4$, 70%.

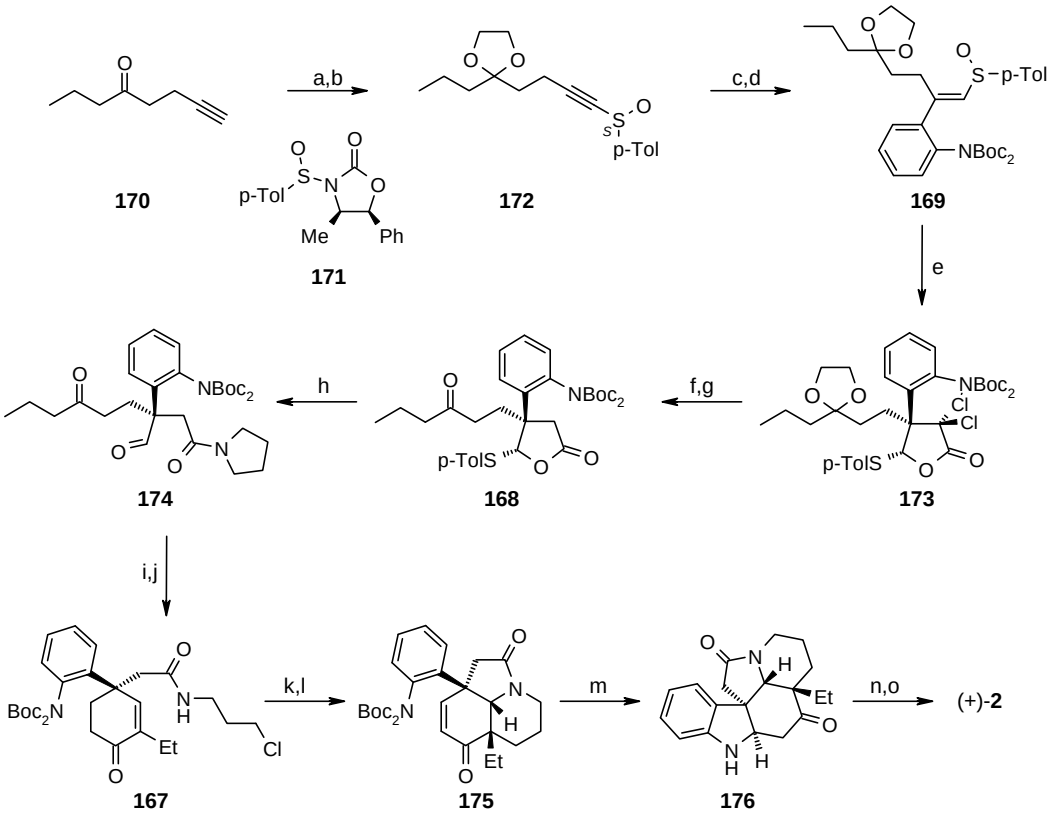
In 2002 Marino *et al.*[34] reported a new strategy for the enantiospecific synthesis of *Aspidosperma* alkaloids resulting in a total synthesis of (+)-aspidospermidine **2**. Their synthesis employed a ketene lactonization reaction of chiral sulfoxide **169**, which enatiospecifically set the critical C5 quaternary carbon centre. Lactone **168** in turn provided enone-amide **167**, setting up a tandem conjugate addition-alkylation sequence on route to (+)-**2** (Scheme 31).



(+)-2 **167** **168** **169**

Scheme 31: Retrosynthetic strategy employed by Marino *et al*.[34]

Their synthesis began with the preparation of enantiomerically pure alkynyl sulfoxide **172** which was then added to the cuprate reagent derived from *ortho*-lithiation of Boc-aniline, to give vinyl sulfoxide **169** after a further Boc protection. The crucial ketene lactonization step was then performed on **169** to afford dichlorolactone **173** which, after dechlorination and deprotection, gave lactone **168**. Opening of the lactone with pyrrolidine next gave aldehyde **174** which underwent intramolecular aldol condensation and amide formation to give cyclohexenone **167**. Exposure of amide **167** to NaH induced a stereoselective tandem conjugate addition/intramolecular alkylation sequence to establish the tetracyclic core of (+)-aspidospermidine **2**, giving enone **175** after oxidation. A sequential deprotection-conjugate addition process then installed the indoline ring giving **176** with all five rings in place. A final reduction strategy completed the total synthesis in 15 steps and 7.9% overall yield (Scheme 32).

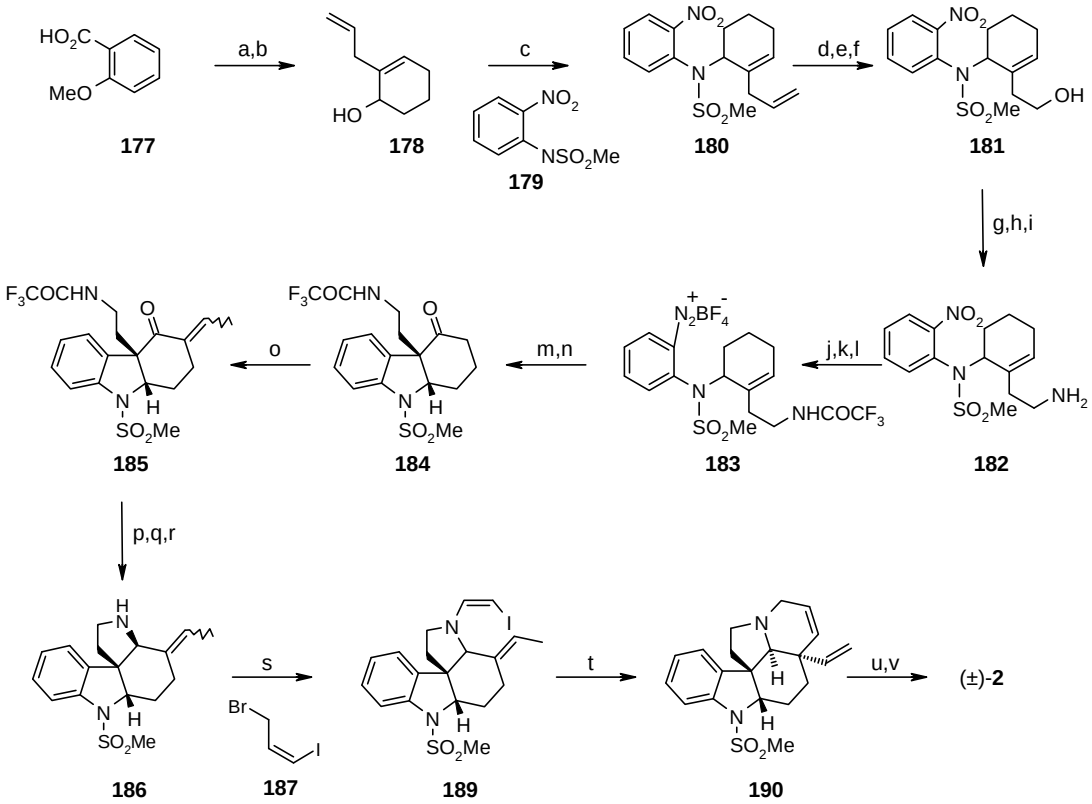


Scheme 32: Marino's total synthesis of (+)-aspidospermidine **2**.[34]

Reagents and conditions: (a) $HOCH_2CH_2OH$, benzene, cat. *p*-TsOH, Δ, 90%; (b) THF, *n*-BuLi, −78 °C, then $MgBr_2$, 0 °C, then **171**, −78 °C, 83%; (c) *t*-BuLi (2 equiv.), CuBr.Me_2S, *N*-Boc-aniline, THF, −78 °C, 82%; (d) MeLi, Boc_2O, THF, −78 °C, 81%; (e) Zn(Cu), Cl_3CCOCl, THF, −45 °C, 78%; (f) *n*-Bu_3SnH, cat. Et_3B, benzene, Δ, 92%; (g) acetone, cat. *p*-TsOH, RT, 96%; (h) pyrrolidine, benzene, RT, 86%; (i) pyrrolidine, 2-propanol, 33% aq. AcOH; (j) *i*-BuOCOCl, NEt_3, 3-chloropropylamine hydrochloride, THF, 0 °C, 64% (2 steps); (k) NaH, DMF, 0 °C, 86%; (l) KHMDS, TMSCl, THF, −78 °C, then $Pd(OAc)_2/O_2$, DMSO, 60 °C, 80%; (m) 3 M HCl, 2-propanol, Δ, 0.5 h, 90%; (n) $H_2NNH_2.H_2O/Na/HOCH_2CH_2OH$, 160 °C, 1 h, then 210 °C, 3 h, 75%; (o) $LiAlH_4$, THF, Δ, 3 h, 90%.

In 1998 and 2000 Murphy and coworkers reported 2 total syntheses of (±)-aspidospermidine.[2,35] Both approaches used radical methodology to install ring B. The first approach used a 12 step procedure to create precursor **183**.[2] Electron transfer from TTF to diazonium salt **183** was followed by loss of dinitrogen to produce an aryl radical intermediate. This underwent cyclisation to install the *cis*-[6,5] ring system (A and B). The resulting alkyl radical was trapped with $TTF^{+\cdot}$ to give a sulfonium salt which underwent uni-molecular solvolysis to yield the intermediate alcohol. Oxidation of the alcohol gave ketone **184** with the ABC

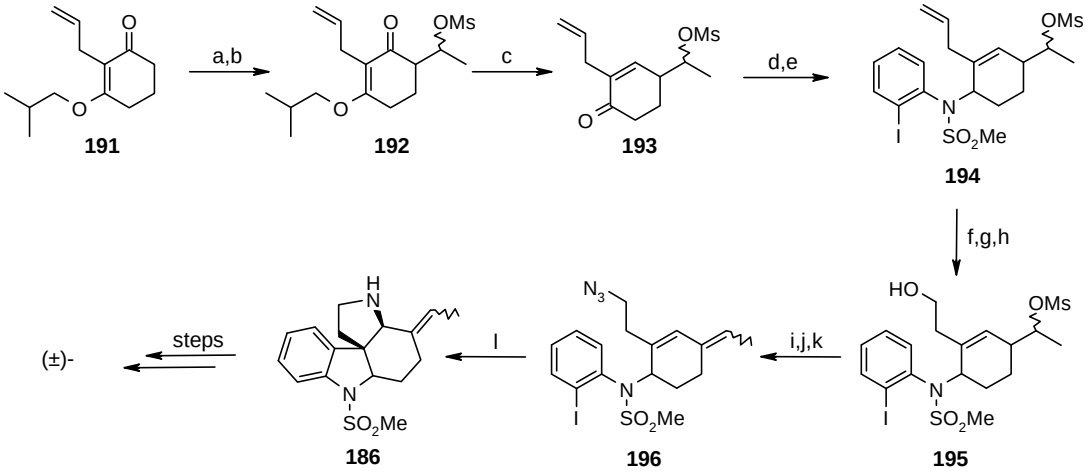
tricycle in place (Scheme 33). A Mukaiyama aldol reaction followed by spontaneous dehydration was then used to install the ethyl side chain giving **185**. Luche reduction of ketone **185** followed by an internal Mitsunobu reaction of the alcohol closed ring E to afford **186** after reductive cleavage of the trifluoroacetamide group. This was followed by alkylation and a palladium-induced D ring closure to afford pentacycle **190**. Hydrogenation of the resultant alkenes followed by deprotection of the methylsulfonyl group completes the total synthesis of (±)-aspidospermidine **2** in 22 steps (Scheme 33).



Scheme 33: Murphy's total synthesis of (±)-aspidospermidine **2**.[2]

Reagents and conditions: (a) NH_3, Na, −78 °C, allyl bromide, −78 °C to RT, HCl, H_2O, Δ, 33%; (b) $CeCl_3$, $NaBH_4$, MeOH, 15 min, 71%; (c) PPh_3, DEAD, THF, 0 °C to RT, **179**, 1 h, 76%; (d) OsO_4, NMO, acetone, H_2O, *t*-BuOH, 20 h, 62%; (e) $NaIO_4$, Et_2O, H_2O, MeOH, 4.5 h, 97%; (f) $NaBH_4$, MeOH, 10 min, 91%; (g) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 19 h, 70%; (h) NaN_3, DMF, 96%; (i) $HSCH_2CH_2SH$, NEt_3, *i*-PrOH, $NaBH_4$, 48 h; (j) $(CF_3CO)_2O$, NEt_3, DMAP, THF, 0 °C to RT, 4 d, 87%; (k) $NaBH_4$, $Cu(acac)_2$, EtOH, 1 h, 70%; (l) $NOBF_4$, CH_2Cl_2, 0 °C, 1 h; (m) TTF, acetone, H_2O, 2 d, 45% (2 steps); (n) PCC, CH_2Cl_2, 18 h, 83%; (o) TMSCl, NEt_3, DMF, 80 °C, 48 h, then $TiCl_4$, paraldehyde, CH_2Cl_2, −78 °C, 30 min, then RT, 48 h, 51%; (p) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C, 100%; (q) DEAD, PPh_2Me, THF, 0 °C to RT, 99%; (r) $NaBH_4$, EtOH, 60 °C, 82%; (s) **187**, K_2CO_3, THF, 80%; (t) $Pd(OAc)_2$, NEt_3, PPh_3, MeCN, Δ, 37%; (u) 10% Pt/C, H_2 40 psi, EtOH, 5 d, 58%; (v) Red-Al, toluene, 100 °C, 84%.

Murphy's second synthesis[35] employed a radical cascade cyclisation to simultaneously construct rings B and E in the target. An aldol condensation between the enolate of **191** and acetaldehyde, followed by mesylation, affords **192** which was further reduced to enone **193** with DIBAL-H. Luche reduction and a Mitsunobu reaction coupling produced sulfonamide **194**. Sequential oxidative cleavage of the terminal alkene, aldehyde reduction to alcohol **195**, elimination of the mesylate, mesylation and azide displacement gave azide **196**. Treatment under radical forming conditions then induced a tandem radical cyclisation to install rings B and E, giving the known tetracycle **186** and intersecting their previous total synthesis (Scheme 34).



Scheme 34: Murphy's second total synthesis of (±)-aspidospermidine **2**.[35]

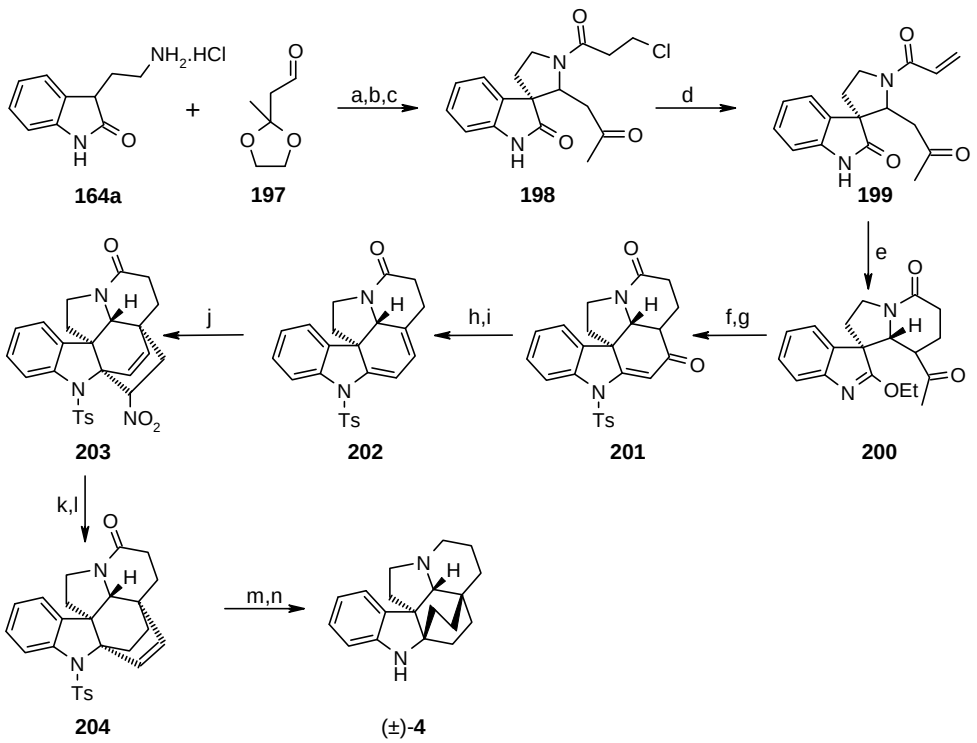
Reagents and conditions: (a) LDA, CH_3CHO, 72%; (b) NEt_3, MsCl, DMAP, CH_2Cl_2, 83%; (c) DIBAL-H, CH_2Cl_2, 67%; (d) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 67%; (e) 2-iodophenylmethanesulfonamide, DIAD, Me_3P, THF, pyridine, 51%; (f) OsO_4, NMO, acetone, H_2O, *t*-BuOH, 78%; (g) $NaIO_4$, Et_2O, H_2O, EtOH, 65%; (h) $NaBH_4$, MeOH, 20 min, 95%; (i) DBU, toluene, Δ, 91%; (j) MsCl, NEt_3, DMAP, CH_2Cl_2, 78%; (k) NaN_3, DMF, 50 °C, 72%; (l) TTMSS, AIBN, benzene, Δ, 40%.

Previous syntheses of aspidofractinine.

In contrast to the numerous syntheses reported for aspidospermidine **2**, the total synthesis of aspidofractinine **4** has been realized on just four occasions. Each is by a different group and employs a strategy successfully employed in a synthesis of aspidospermidine **2**.

Ban's early contribution.

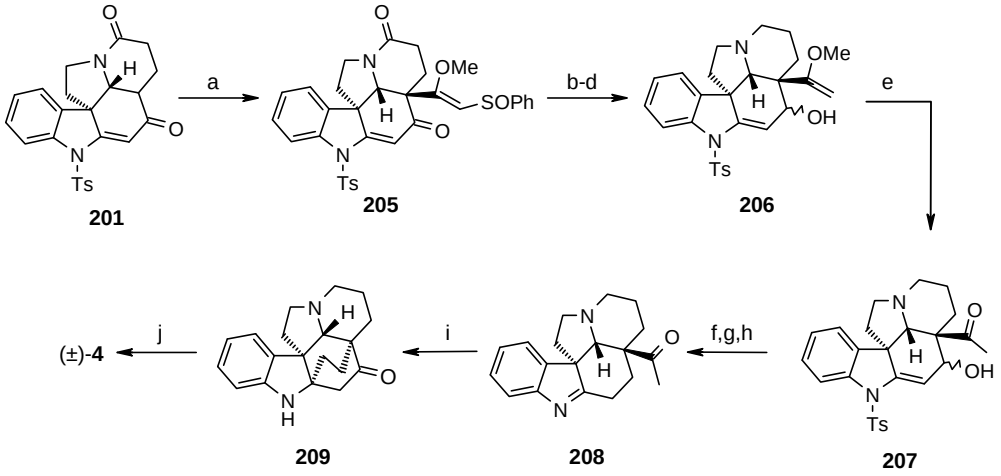
Ban and co-workers were one of the first groups to develop an approach to the pentacyclic ABCDE ring system of the *Aspidosperma* family of alkaloids. Eleven years later they were the first to achieve a total synthesis of aspidofractinine **4**.[36] Ban's synthesis began with 2-hydroxytryptamine hydrochloride **164a** which was condensed with 3-oxobutanal ethylene ketal **197** to give tricyclic oxindole **198**. A Michael-type intramolecular cyclisation next installed ring D giving **200**. Treatment with NaH in refluxing DMSO for 60 hours followed to close ring C, giving pentacycle **201** after tosylation. Reduction of ketone **201** and subsequent dehydration furnished diene **202** which was then subjected to a Diels-Alder cycloaddition with nitroethylene, installing the final F ring to give **203**. Further functional group manipulations accomplished the total synthesis of (±)-aspidofractinine **4** (Scheme 35).



Scheme 35: Ban's first total synthesis of (±)-aspidofractinine **4**.[36]

Reagents and conditions: (a) basic aq. EtOH, 63%; (b) β-chloropropionyl chloride; (c) H_3O^+; (d) EtOH, CH_2Cl_2 NaOH, RT, 12 h, 89%; (e) $Et_3O^+BF_4^-$ (6 equiv.), 1,2-dichloroethane, 65 °C, 20 h, 51%; (f) NaH, DMSO, Δ, 60 h, 50%; (g) TsCl, CH_2Cl_2; (h) $NaBH_4$, EtOH, THF, RT, 87%; (i) pyridine, PBr_3, benzene, RT, 74% (j) nitroethylene, CH_2Cl_2, RT, 12 h, 80%; (k) H_2 (5.3 atm), PtO_2, 90%; (l) sodium nitrate, aq. AcOH, 55 °C, 5 h, 43%; (m) $LiAlH_4$, 1,2-dimethoxyethane, Δ, 3 h; (n) H_2, Pt, EtOAc, 100% (2 steps).

Some 10 years later, Ban and co-workers reported an adaptation of their first total synthesis from the common intermediate **201**.[37] The two carbon Michael-acceptor chloromethoxyvinyl sulfoxide was introduced onto ketone **201** using LiHMDS to give **205**. Reduction and desulfurization produced enol ether **206**, a precursor to allylic alcohol **207**. A short reduction sequence then afforded unstable indolenine **208** which, when treated with dilute HCl at 110 °C, smoothly underwent cyclisation to produce the hexacyclic ring system **209**. Finally, reductive removal of the ketone moiety gave the natural product (±)-**4** (Scheme 36).



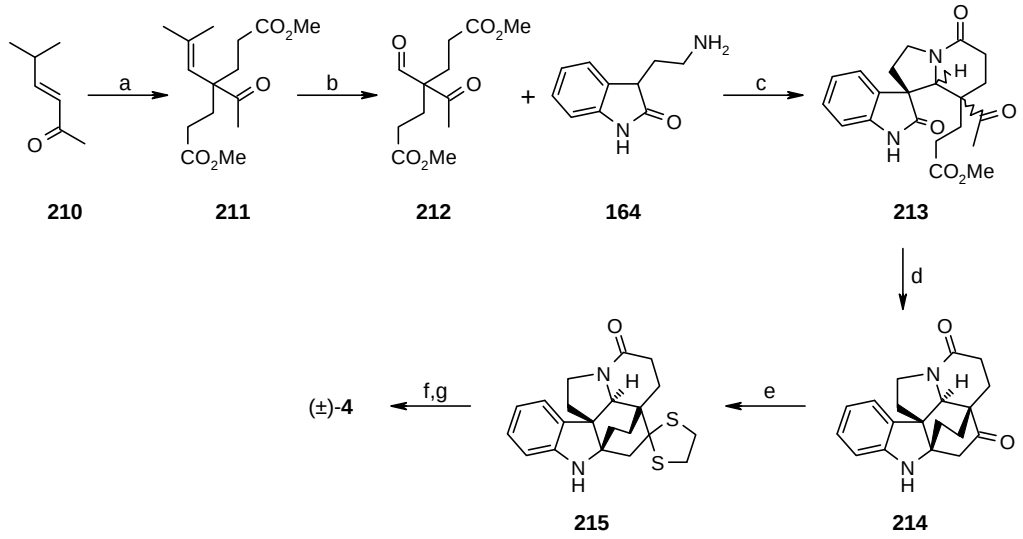
Scheme 36: Ban's second total synthesis of (±)-aspidofractinine **4**.[37]

Reagents and conditions: (a) LiHMDS, THF, −78 °C; PhSOCH=C(Cl)OMe, 60%; (b) P_4S_{10}, THF, Δ, 78%; (c) Raney nickel, THF, Δ, 67%; (d) $LiAlH_4$, THF, −50 °C; (e) aq. H_2SO_4, THF, 86% (2 steps); (f) $SOCl_2$, pyridine, CH_2Cl_2, −50 °C, 30 min then $NaHCO_3$, 53%; (g) Pt, H_2, EtOAc, 100%; (h) Na-naphthalene, THF, −78 °C, 50%; (i) dilute HCl, 110 °C, 1.5 h, 90%; (j) Huang-Minlon reduction, 74%.

Levy and Cartier's total synthesis.

In 1989 Levy and Cartier reported a total synthesis of aspidofractinine **4** which combined their acid induced cyclisation/decarboxylation protocol[32,38] (used towards aspidospermidine **2** with Ban's intramolecular cyclisation of a methyl ketone to an oxindolic lactam[36] to install the hexacyclic framework of the natural product. Key intermediate **213** was established through the condensation of aldehyde **212** and amine **164** to install rings ABDE. Double cyclisation of **213** to **214** was achieved by treatment with *p*-TsOH in refluxing toluene and is thought to proceed *via* initial cyclisation of the methyl ketone onto the oxindole ring followed by

decarboxylative cyclisation of the ester side chain. Ketolactam **214** was sequentially reduced (*via* the thioketal **215**) to complete the total synthesis of (±)-aspidofractinine **4** in 7 steps and 1.4% overall yield (Scheme 37).

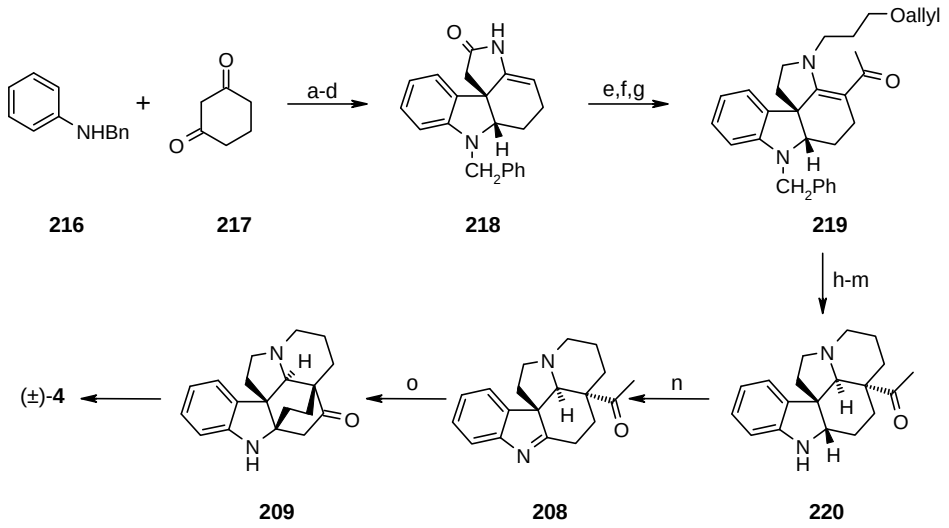


Scheme 37: Levy's total synthesis of (±)-aspidofractinine **4**.[38]

Reagents and conditions: (a) methyl acrylate, benzene, Triton-B (cat.), K_2CO_3, Δ, 20 h, 26%; (b) ozonolysis, 65%; (c) toluene, Δ, Dean & Stark, 2 h, then AcOH, Δ, 5 h, 40%; (d) *p*-TsOH, toluene, Δ, 50%; (e) ethanedithiol, AcOH, BF_3, RT, 12 h, 70%; (f) Raney nickel, EtOH, 87%; (g) $LiAlH_4$, 70%.

Gramain's formal total synthesis.

Gramain's[39] 15 step formal synthesis of (±)-aspidofractinine **4** followed the common strategic plan to install the F ring but builds up the pentacyclic framework (ABCDE) in a unique way. Enamide **218** was synthesized in 4 steps from benzyl protected aniline **216** and 1,3-cyclohexanedione **217** to give the tetracycle **218**. The necessary carbons for ring D were then introduced *via* *N*-alkylation of **218**. Subsequent functional group manipulation allowed D ring closure through intramolecular cyclisation to give pentacycle **220** from **219**. The total synthesis was completed by hydrogenolysis of the residual *N*-benzyl group, Swern oxidation to indolenine **208** and cyclisation to **209** (Scheme 38). Reduction of **209** to (±)-**4** had been accomplished by Ban *et al*.[37] so therefore Gramain's work completed a formal total synthesis.

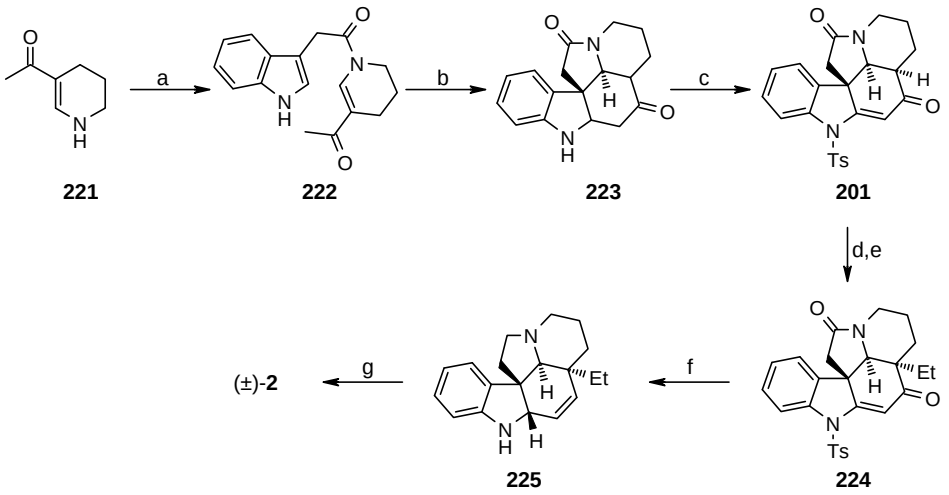


Scheme 38: Gramain's total synthesis of (±)-aspidofractinine **4**.[39]

Reagents and conditions: (a) *p*-TSA, toluene, Δ, Dean-Stark, 8 h, 97%; (b) benzene, irradiation, 1 h, 95%; (c) KH, THF, iodoacetamide, 30 min, RT, 93%; (d) camphorsulfonic acid, CH_2Cl_2, molecular sieves, Δ, 8 h, 100%; (e) KH, THF, $I(CH_2)_3$-*O*-allyl; (f) $LiAlH_4$, THF, Δ; (g) CH_3COCl, NEt_3, CH_2Cl_2, 72% (3 steps); (h) $LiAlH_4$, THF, 20 °C, 5 min, 60%; (i) DABCO, $RhCl_3$, EtOH, H_2O; (j) H_3O^+, EtOH, H_2O; (k) TsCl, pyridine, 48 h, 0 °C; (l) NaH, benzene, Δ, 20%; (m) H_2, Pd/C, EtOH, $CHCl_3$; (n) $(COCl)_2$, DMSO, NEt_3; (o) HCl, MeOH, Δ, 85% (3 steps).

Wenkert's joint total synthesis of (±)-aspidospermidine and (±)-aspidofractinine.

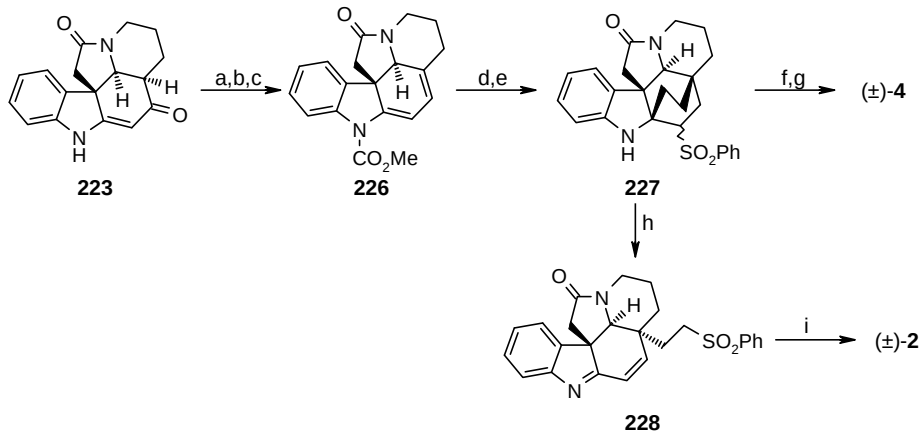
In 1991 Wenkert reported his second total synthesis of aspidospermidine **2**,[40] followed in 1994 by a unified approach to aspidospermidine **2** and aspidofractinine **4**.[41] Thus a total synthesis of aspidospermidine **2**[40] was accomplished through the rapid construction of the natural skeleton from indoleacetic anhydride and piperidine **221** giving, after cyclisation, **223**. Following oxidation to **201**, the ethyl side chain was installed by treatment with KH, LiI and EtI to give **224**. *N*-Deprotection and exhaustive reduction of the carbonyl groups gave **225** which, on hydrogenation gave (±)-aspidospermidine **2** to complete a 7 step total synthesis in 6.5% overall yield (Scheme 39).



Scheme 39: Wenkert's second total synthesis of (±)-aspidospermidine **2**.[40]

Reagents and conditions: (a) indolacetic anhydride, THF, RT, 24 h, 71%; (b) $BF_3.Et_2O$, 85 °C, 10 min, 42%; (c) lead tetraacetate, CH_2Cl_2, Δ, 15 min, 85%; (d) *n*-BuLi, TsCl, THF, 92%; (e) KH, LiI, EtI, THF, 52%; (f) $LiAlH_4$, THF, Δ, 65%; (g) H_2, Pt/C, THF, 40 psi, 82%.

The key intermediate **223** was also transformed into diene **226** in 3 steps. A Diels-Alder cycloaddition reaction between this and phenyl vinyl sulfone installed ring F, furnishing hexacycle **227**. Raney nickel and $LiAlH_4$ reductions gave aspidofractinine **4**. Alternatively, treatment of **227** with ethylene glycol and *t*-BuOK induces fragmentation of the F ring to give pentacycle **228**. Reduction with $LiAlH_4$ provided (±)-aspidospermidine **2** (Scheme 40).

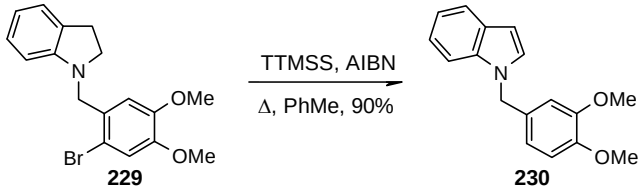


Scheme 40: Wenkert's synthesis of aspidospermidine **2** and aspidofractinine **4**.[41]

Reagents and conditions: (a) *n*-BuLi, MeOCOCl, THF, 87%; (b) $NaBH_4$, $CeCl_3$, MeOH, 79%; (c) $Et_2O.BF_3$, 88%; (d) phenyl vinyl sulfone, benzene, 4 d, 120 °C, 75%; (e) EtSLi, HMPA, THF, 93%; (f) Ni, isopropanol, 88%; (g) $LiAlH_4$, THF, 76%; (h) *t*-BuOK, $HOCH_2CH_2OH$, 150 °C, 87%; (i) $LiAlH_4$, THF, 74%.

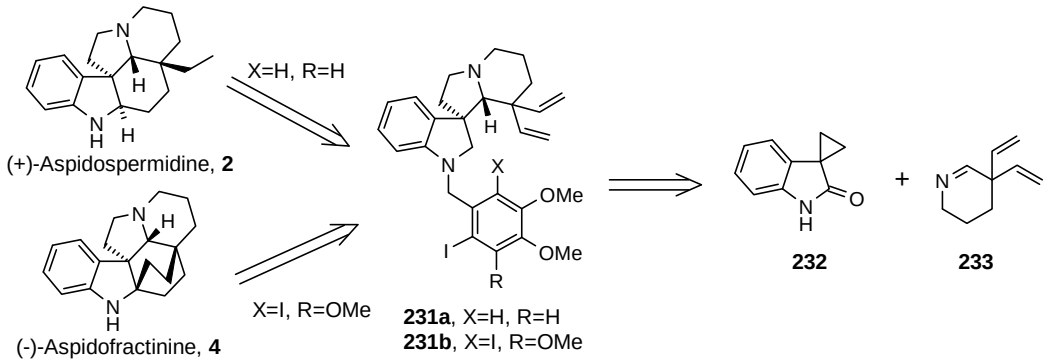
Our approach

Our approach to aspidospermidine **2** and aspidofractinine **4** drew inspiration from an unlikely source. Previous work within our group had shown that treatment of indoline **229** under radical forming conditions (TTMSS, AIBN, Δ, PhMe) created indole **230** (Scheme 41). This result showed that translocation of an aryl radical to C2 of an indoline was both fast and efficient. We believed that such alkyl radicals could provide a way of elaborating the C2 position of an indoline under very mild conditions.



Scheme 41

Extrapolation of this result to the targets led us to an unusual disconnection for the *Aspidosperma* alkaloids in which a halogenated arene attached to the indoline nitrogen is used to activate the proximal methylene unit (Scheme 42). We believe that an aryl radical generated from **231a** would induce 1,5-*H* atom abstraction, resulting in translocation to C2 of the indoline. In turn, this would readily undergo a 6-*endo*-trig cyclisation to the proximal alkene to establish the [6.5.6.6.5] ring system of aspidospermidine **2** after hydrogenolysis. Importantly, by employing the same reaction conditions with di-iodide **231b**, it should be possible to achieve double activation of the methylene group and a tandem radical translocation-cyclisation sequence leading to aspidofractinine **4**.



Scheme 42: Retrosynthesis of our proposed approach to aspidospermidine **2** and aspidofractinine **4**.

The key intermediate **231** could in turn be obtained by ring opening of cyclopropane **232** with imine **233**. At first sight our suggestion that the radical cyclisation strategy will follow a 6-*endo*-trig cyclisation mode rather than the more usual 5-*exo*-trig pathway seems counterintuitive. However, we believe that the molecule's rigid framework makes it easier to adopt a reactive conformer placing the terminal carbon of the acceptor alkene close to the C2 radical centre.

Our approach follows a unique strategy establishing the ABDE ring system initially before closing ring C (or rings C and F) using radical intermediates. Many of the previously reported routes have the C ring completed early in the synthetic strategy i.e. Fischer indole[12], Harley-Mason rearrangement[13] and the E ring closing strategies.[25-31] Those that do have the ABDE ring system established use indole (Wenkert[40]) and oxindole (Laronze[32], Ban[36], Levy[38]) centres to achieve closure of ring C. Our strategy allows the ABDE system to be established in one reaction giving a common precursor **231** to both aspidospermidine **2** and aspidofractinine **4**.

Radical methodology

Selective and direct activation of C-H bonds to allow replacement with new C-C bonds represents an important and long term goal in organic chemistry. Selective functionalisation of sp^3 C-H bonds could, in principle, allow targets to be synthesized with minimal functionalisation and maximum atom economy. One such way of elaborating C-H bonds is *via* radical translocation. The term 'radical translocation' is applied to reactions involving intramolecular abstraction of a hydrogen atom by a radical centre resulting in the relocation of the radical site. The new radical can then be used to elaborate positions which are unreactive to selective modification. H-atom abstraction generally occurs at a position 5 centres removed from the initial radical to accommodate the stereoelectronic preference for a X---H---C 'bond' angle close to 180° (Figure 5).[42] The translocation step is driven by the formation of a more stabilized radical species and the creation of a relatively strong bond (e.g. Ar-H) at the expense of that which is broken (e.g. alkyl-H).

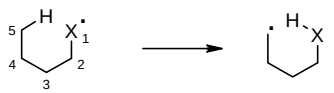
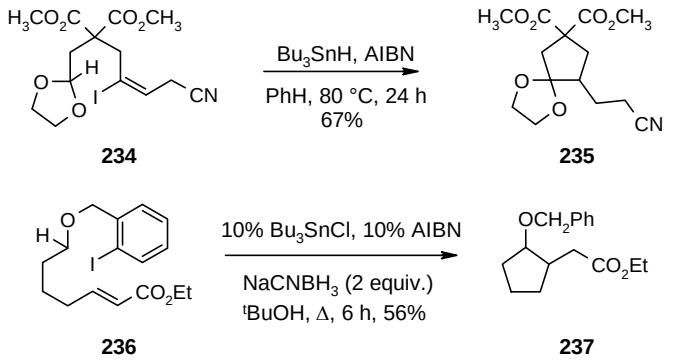


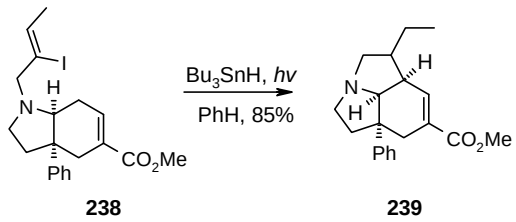
Figure 5: Radical translocation by 1,5-*H* atom abstraction.

In 1988 Curran[43] and Parsons[44] independently reported examples of radical translocation being used for C-C bond formation. Curran and co-workers showed that vinyl halide **234**, on treatment with tri-butyltin hydride, under standard radical forming conditions, readily forms a reactive vinyl radical. 1,5-*H*-atom abstraction from the proximal acetate provides an alkyl radical centre able to undergo cyclisation to the acceptor alkene giving **235**. The acetal group acts as a radical stabilizing group, weakening the C-H bond sufficiently to allow the chain reaction to propagate. Curran cleverly extended this tactic, by employing a modified protecting group, benzyl iodide, to act as the initiating radical intermediate. For example, the alkyl derived from **236** readily promotes 1,5-*H* atom abstraction from a proximal ethereal carbon, inducing cyclisation to **237**. This leaves a simple benzyl group which can be removed by hydrogenolysis to reveal an alcohol (Scheme 43).



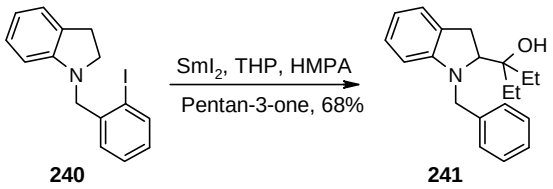
Scheme 43: Curran's radical translocation methodology.[43]

Contemporaneously, Parsons and Lathbury[44] reported a radical cyclisation route to the pyrrolizidine ring system involving formation of a vinyl radical from **238**. 1,5-*H* atom abstraction from the allylic methylene was followed by a 5-*exo*-trig cyclisation to the pendant double bond leading to **239** (Scheme 44).



Scheme 44: Parsons' abstraction-addition sequence.[44]

In 1995 Undheim employed *o*-benzylhalides to initiate translocation to C2 of an indoline using samarium(II) iodide (Scheme 45).[45] In this case the α-aminyl radical is then reduced to a presumed α-amino samarium(III) intermediate which is trapped by the addition of the ketone to give alcohol **241** in a radical-polar crossover reaction.



240 **241**

Scheme 45: Undheim's approach to α-substituted amines.[45]

The above results provide some precedence for our key step, and demonstrate the potential of radical translocation in the functionalisation of remote carbon centres, including the 2-position of an indoline centre.

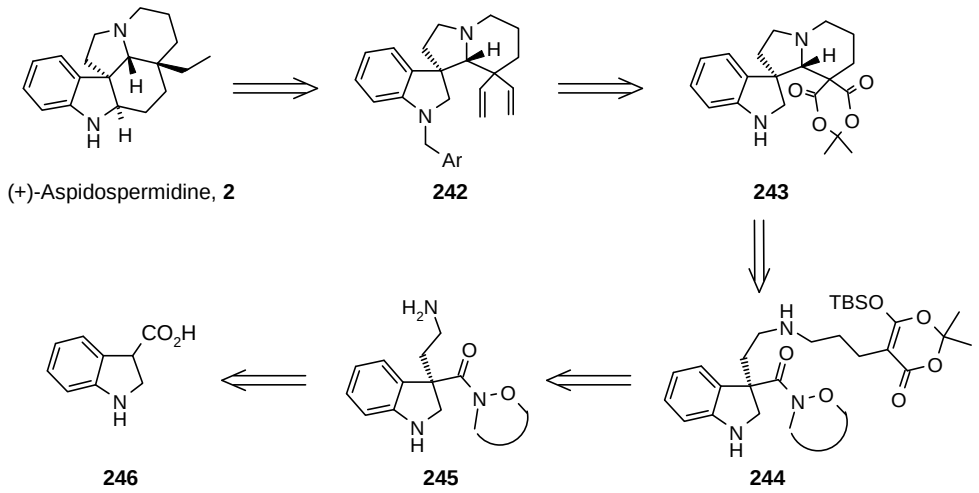
Aims and objectives

Our goal is to complete short and efficient total syntheses of aspidospermidine **2** and aspidofractinine **4**. Key steps include cyclopropane opening with imine **233** to prepare key intermediate **231** and the aforementioned radical translocation/cyclisation sequence to achieve CH activation and CH_2 double activation in pursuit of the targets. The radical methodology will also be investigated to further explore the chemistry of the 2-indoine radical.

Chapter 2 – Establishing the ABDE Ring Core

Early Approaches

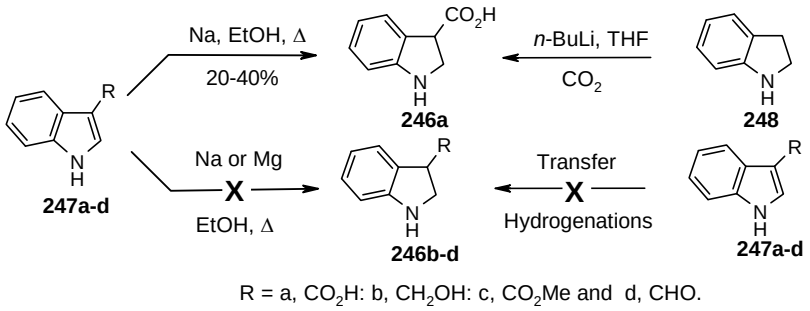
The first phase of our program was concerned with establishing the ABDE ring system common to aspidospermidine **2**, aspidofractinine **4** and the intermediate (**242**) for our key radical translocation step. Our primary plan was to construct the tetracyclic system **242** from the C3 substituted indoline **246** *via* amines **245** and **244** (Scheme 46).



Scheme 46: Retrosynthetic analysis for construction of the ABDE ring framework.

Following introduction of the quaternary centre at C3, our plan envisioned a condensation between **245** and an aldehyde side chain unit with the carbon chain required for construction of rings D and E. Reduction of the Weinreb amide in **244** provides an aldehyde which we hoped would react spontaneously with the proximal amine to close ring E. The resulting iminium ion intermediate would in turn be trapped by the incorporated silyl enol ether closing ring D to give spirocycle **243**. The diene unit could then be incorporated, facilitating the radical cyclisation to close the final ring (Scheme 46).

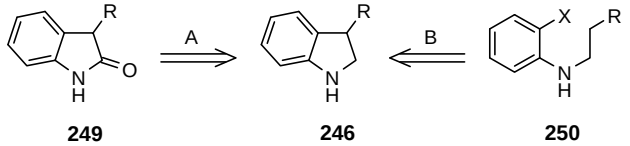
Indoline-3-carboxylic acid **246**, the proposed starting material for this sequence, was not commercially available and consequently our attention turned to methods for its synthesis. Examination of the literature provided only one documented preparation from Wolf *et al*. in 1972.[46] They synthesized the indoline *via* a Birch-style reduction of 3-indole carboxylic acid **247a** using sodium in anhydrous ethanol (Scheme 47).



Scheme 47: Early approaches towards C3 substituted indolines.

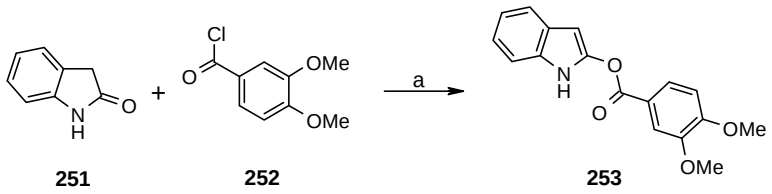
In our hands the reduction was successful in furnishing the target, but proved capricious, low yielding (20-40%), difficult to perform and unsuitable for scale-up. Isolation and purification also proved problematic prompting us to examine the dissolving metal reduction conditions to the corresponding alcohol, ester and aldehyde derivatives **247b-d**. Sodium and magnesium were both examined as reducing agents, though without success. Attention next turned to the possibility of effecting hydrogenation of the indole. Reductions of this type are known to proceed under forcing conditions of high pressure and temperature where over-reduction is often a problem.[47] Transfer hydrogenations have also been reported with functionalized indoles,[48] wherein protonation at C3 initially gives a 3*H*-indolium cation which is then attacked by the hydride source. Reported methods include: triethylsilane and TFA, $NaB(CN)H_3$ and AcOH, BH_3.DMS and TFA and Pd/C and formic acid.[48] These conditions were each applied to alcohol **246b**, ester **246c** and aldehyde **246d** without success. Only Pd/C with formic acid succeeded in reducing the indole, but this caused decarboxylation at C3 so was of no practical use. Direct lithiation-addition protocols were also attempted but to no avail (Scheme 47).

With direct methods of preparing the required 3-substituted indoline proving unproductive, our attention turned to two alternative approaches. In the first we sought to use an oxindole core to elaborate C3; while in the second we sought to build the indoline core from an acyclic precursor (Scheme 48).



Scheme 48: Retrosynthetic approach towards C3 substituted indolines.

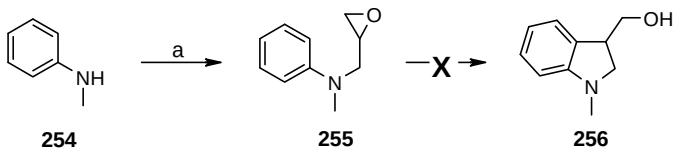
Initial attempts to elaborate oxindole **251** proved unsuccessful. Though the C2 carbonyl increased acidity at C3 we encountered intractable selectivity problems between *N*, C3 alkylation and *O*-alkylation (e.g. Scheme 49).



Scheme 49: Oxindole selectivity problems.

Reagents and conditions: (a) NEt_3, CH_2Cl_2, RT, 48 h, 34%.

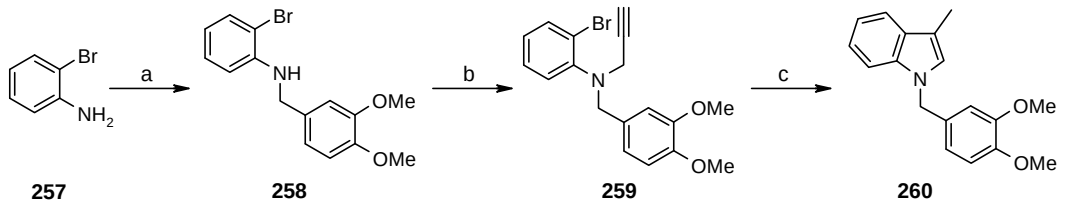
Formation of the indoline unit from acyclic precursors was investigated in numerous experiments, including the potential Lewis acid mediated opening of epoxide **255**.[49] Epoxide **255** was formed from *N*-methylaniline **254** in 73% yield by alkylation with epibromohydrin. Unfortunately only starting epoxide **255** was recovered when treated with a variety of Lewis acids, with forcing conditions yielding complex product mixtures (Scheme 50).



Scheme 50: Epoxide opening.

Reagents and conditions: (a) K_2CO_3, epibromohydrin, EtOH, Δ, 5 h, 73%.

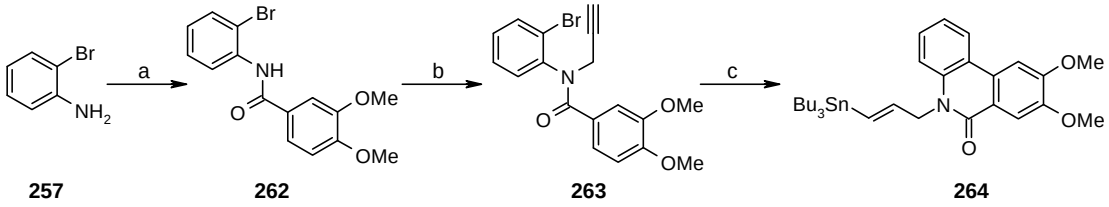
Radical cyclisation methodologies were also investigated, following an approach reported by Boger and Coleman.[50] The radical precursor **259** was prepared from 2-bromoaniline **257** by sequential benzylation with 3,4-dimethoxybenzyl bromide **261** (to **258**) and alkylation with propargyl bromide (Scheme 6). Treatment of **259** under radical forming conditions, tributyltin hydride and VAZO in refluxing toluene, initiated C-Br homolysis and 5-*exo*-dig cyclisation of the resultant aryl radical. Rapid isomerisation of the resultant *exo*-cyclic alkene followed to give indole **260** as the major product in 90% yield.



Scheme 51: Radical cyclisation.

Reagents and conditions: (a) NaH, DMF, 3 h, RT, then BnBr **261**, 90 °C, 16 h, 67%; (b) NaH, DMF, RT, 4 h, then propargyl bromide, 60 °C, 72 h, 55%; (c) *n*-Bu_3SnH, VAZO, PhMe, Δ, 48 h, 90%.

In the hope of preventing isomerisation of the *exo*-cyclic alkene the *N*-protecting group was modified to an amide moiety. Treatment of amide **262** with propargyl bromide gave the radical precursor **263** in 86% yield. When treated under the aforementioned radical forming conditions, **263** unexpectedly yielded tricycle **264** indicating that the 6-*exo/endo*-trig cyclisation to the arene moiety was faster than the corresponding 5-*exo*-dig cyclisation to the alkyne (Scheme 52)!



Scheme 52: Radical cyclisation.

Reagents and conditions: (a) NEt_3, CH_2Cl_2, RT, 16 h, 81%; (b) NaH, DMF, RT, 4 h, then propargyl bromide, RT, 16 h, 86%; (c) *n*-Bu_3SnH, VAZO, PhMe, Δ, 48 h, 32%.

Curran and Jones[51,52] have both reported interesting findings in the radical cyclisation reactions of substituted anilides. In systems such as **263** the aryl radical, resulting from C-Br homolysis, has the choice of reacting with the functional group in the carbon substituent of the amide (in this case the electron-rich aryl) or in the other *N*-substituent (alkyne), leading potentially to a complex product mixture. The product ratios obtained were determined by the conformational preference of the starting material, with Curran and Jones both finding an overwhelming preference for one product in most cases. The anilide systems investigated had two significant factors contributing to their preferred conformation: (1) restricted rotation about the

C-N bond of the amide, and (2) restricted rotation about the aryl C-N bond (atropisomerism). The short lifetime of the unstable aryl radical means there is no time for rotation around either of these restricted bonds before cyclisation occurs; therefore the regioselectivity of the reaction is predetermined by the lowest energy conformation of the starting material.

N-aryl amides have a preference to exist in an *E* geometry, placing aryl and O *anti* to one another. Thus, with regard to the amide rotatmers, conformers **263-C** and **263-D** are lower in energy than **263-A** and **263-B** (Figure 6). On the radical cyclisation timescale the amide C-N geometry is essentially fixed. On consideration of the amide rotamers alone, the aryl radical can still potentially add to the alkyne or arene through rotation of the aryl C-N bond.

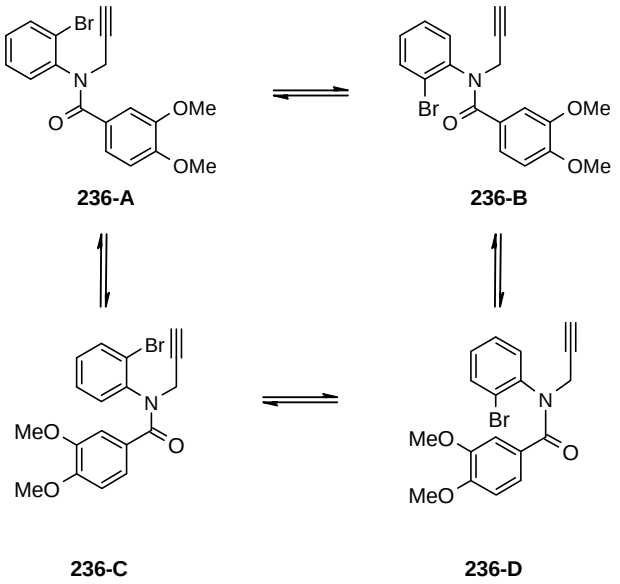
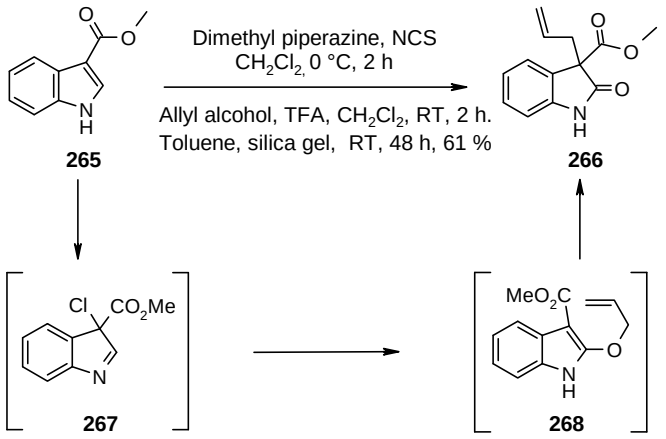


Figure 6: Conformations of amide **236**.

It is known that *ortho*-substituted anilides are chiral by virtue of the *N*-aryl twist and have significant rotational barriers.[53] The extent of the twist is determined by the competition between the need for planarity to allow resonance stabilization of the nitrogen lone pair into the aromatic ring and the severe steric interactions between the *ortho*-halide and the amide substituent which favours a perpendicular orientation. The resulting chirality induced by this twisted conformation is seen in the ^{1}H NMR spectrum of **263**, which shows the diastereotopic nature of the NCH_2 hydrogens showing as two separate signals (5.09 (1H, b d, *J*=17.4 Hz, HC≡CC**H**H), 4.12 (1H, dd, *J*= 17.4, 2.4 Hz, HC≡CCH**H**)).

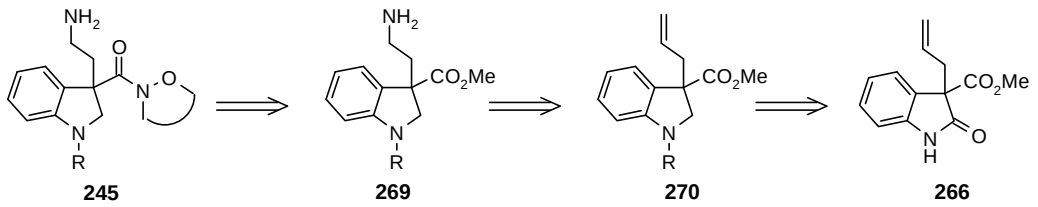
Energetic maxima are expected at planar conformations where steric interactions are maximized and therefore regioselectivities shown during the radical cyclisation are due to the conformer with the least enathalpic and entropic costs. Curran suggested, on the basis of previous work,[51,53] that there was an overwhelming preference for the aryl radical to react with the functional group in the amide side chain, which suggests that in our system **263-D** is the lowest energy conformer, leading to the regioselectivity seen.

With the C3-substituted indoline still evading us, our attention turned to an NCS-promoted oxidative alkylation procedure developed by Booker-Milburn *et al*.[54] They had shown that the commercially available methyl indole-3-carboxylate **265** is readily transformed into oxindole **266**, with a Claisen rearrangement generating a quaternary centre at C3 (Scheme 53).



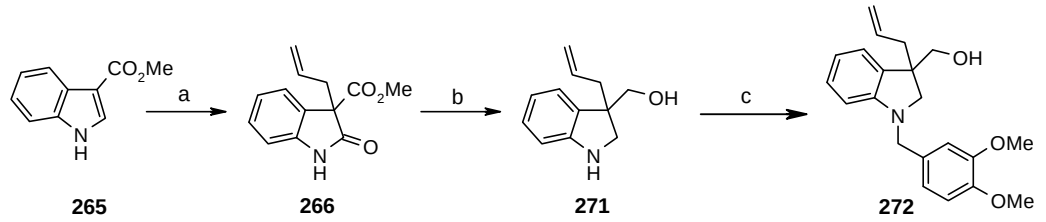
Scheme 53: Booker-Milburn's addition-Claisen rearrangement sequence.[54]

We believed that reduction of the oxindole centre and subsequent manipulation of the C3 groups would provide access to our target indoline **245** (Scheme 54).



Scheme 54: Retrosynthetic approach towards C3 elaborated indoline **245**.

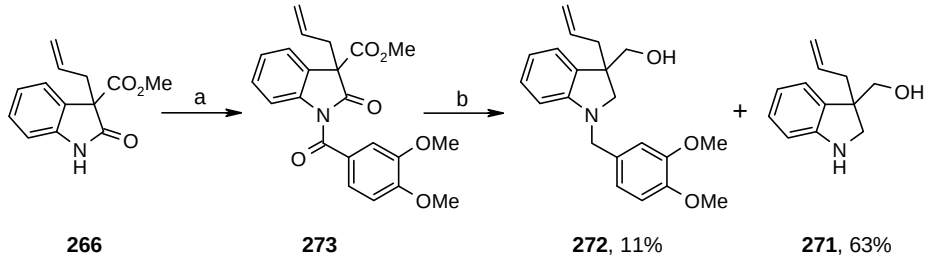
In our hands the NCS promoted Claisen sequence proceeded smoothly to give oxindole **266** in 61% (Scheme 55). Reduction of the product with $LiAlH_4$ produced alcohol **271** in 43% yield together with significant amounts of decarboxylated by-products. Attempts to protect the resultant indoline as its 3,4-dimethoxybenzyl ether proved low yielding (18%), prompting an examination of an array of related strategies.



Scheme 55: Booker-Milburn addition-Claisen rearrangement.

Reagents and conditions: (a) Dimethyl piperazine, NCS, CH_2Cl_2, 0 °C, 2 h, then, allyl alcohol, TFA, CH_2Cl_2, RT, 2 h, then, PhMe, silica gel, RT, 48 h, 61%; (b) $LiAlH_4$, THF, Δ, 24 h, 43%; (c) NaH, DMF, 3,4-dimethoxybenzyl bromide **261**, RT, 16 h, 18%.

It was hoped that *N*-benzylation of indoline **266** would be an efficient process. Alas, protection with 3,4-dimethoxybenzoyl chloride proceeded in a disappointing 10% yield. Global reduction of the oxindole, ester and amide functionality of **273** with $LiAlH_4$ did produce the desired protected indoline **272** albeit in 11% yield. The major product of the reaction was indoline **271** which was formed in 63% yield (Scheme 56).

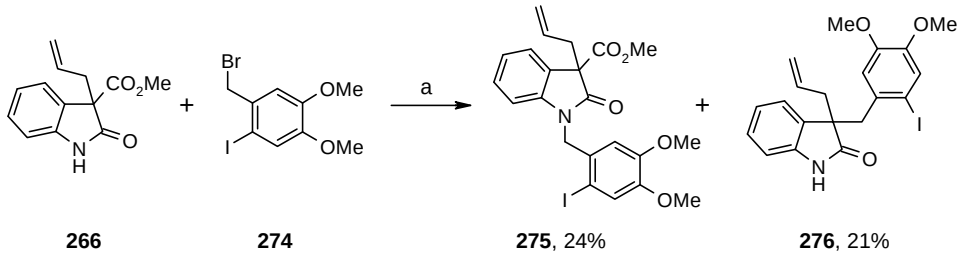


Scheme 56: Reduction problems.

Reagents and conditions: (a) 3,4-dimethoxybenzoyl chloride, NEt_3, CH_2Cl_2, RT, 16 h, 10%; (b) $LiAlH_4$, THF, Δ, 16 h.

The ease of C3-decarboxylation proved a constant burden in our investigation. For example, our attempt to effect the protection of oxindole **266** with benzyl bromide

274 gave rise to a complex product mixture from which two components were isolated. These were identified as the desired *N*-protected oxindole **275** (24%) and oxindole **276** (21%). The latter results from decarboxylation at C3 and benzylation of the resulting enolate (Scheme 57).

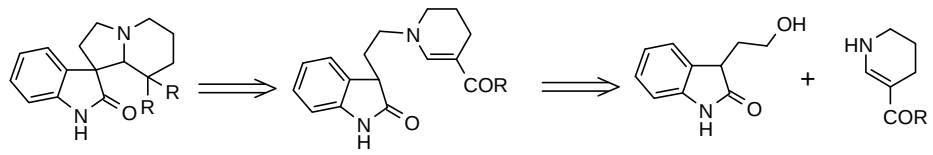


266 **274** **275**, 24% **276**, 21%

Scheme 57: Attempted benzylation of **266** with **274**.

Reagents and conditions: (a) NaH, DMF, RT, 16 h.

A re-evaluation of the problems encountered with the oxindole system led us to consider whether we could use the C3-decarboxylation issues to our advantage. The ease with which decarboxylation occurs provides a good indication of the stability of the resulting enolate. Intercepting this with a suitable Michael acceptor provides a potential pathway to the required ABDE ring system (Scheme 58).

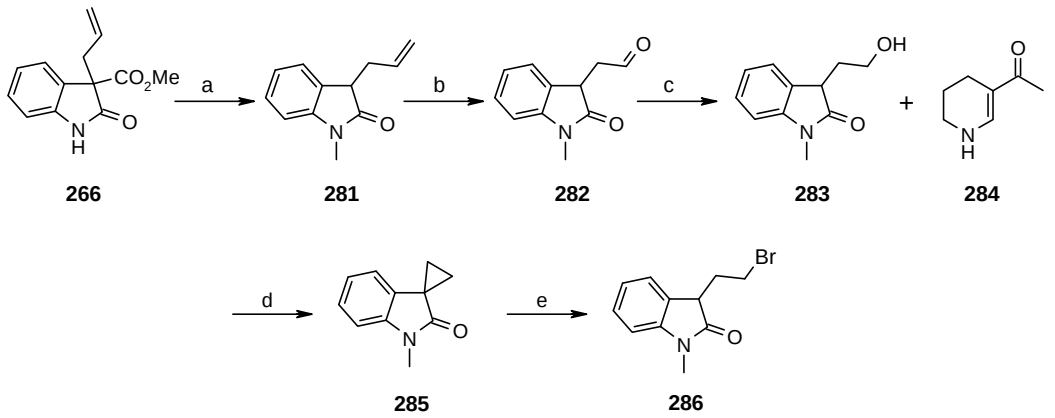


277 **278** **279** **280**

Scheme 58: Retrosynthetic route from oxindole **279**.

Thus, oxindole **266** was subjected to the decarboxylating conditions of NaBr in refluxing DMF. The major product obtained was the *N*-methylated oxindole **281** highlighting the nucleophilicity of the oxindole nitrogen. Ozonolysis of the resultant alkene gave aldehyde **282**, which was subsequently reduced to alcohol **283** using $NaBH_4$. A Mitsunobu reaction was then examined in the hope of conjoining alcohol **283** and enamine **284**. However, treatment with DIAD and PPh_3 in THF produced cyclopropane **285** as the only significant product of the reaction, along with recovered starting materials. This was undoubtedly formed *via* an intramolecular

Mitsunobu reaction between the activated alcohol and the enolate of **283** (Scheme 59).



Scheme 59: Synthetic route towards cyclopropane **285**.

Reagents and conditions: (a) NaBr, DMF, Δ, 2 h, 51%; (b) O_3, CH_2Cl_2, -78 °C, PPh_3, 1 h, 55%; (c) $NaBH_4$, MeOH, RT, 1 h, 58%; (d) DIAD, PPh_3, THF, RT, 16 h, 55%, (e) HBr, AcOH, RT, 6 h, 70%.

The Mitsunobu Reaction

Since its discovery in 1967[55] the Mitsunobu reaction has found wide spread use in many fields due to its versatility and high reliability. The reaction couples an alcohol with an acid/pronucleophile in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine. The reaction proceeds with inversion of the alcohol stereocentre and can utilize a range of range of nucelophilic partners including acids, phenols, diols and imides. The reaction mechanism has been widely studied. The generally accepted mechanism with DEAD and PPh_3 is shown in Figure 7. Reaction of DEAD and triphenylphosphine produce a betaine intermediate **A** which reacts with the alcohol component to yield anion **B** and phosphonium **C**. Proton abstraction by anion **B** on the nucleophilic partner yields Nu- which attacks phosphonium **C**, displacing triphenylphosphine oxide, to give the coupled product that has inverted stereochemistry relative to the alcohol starting material.

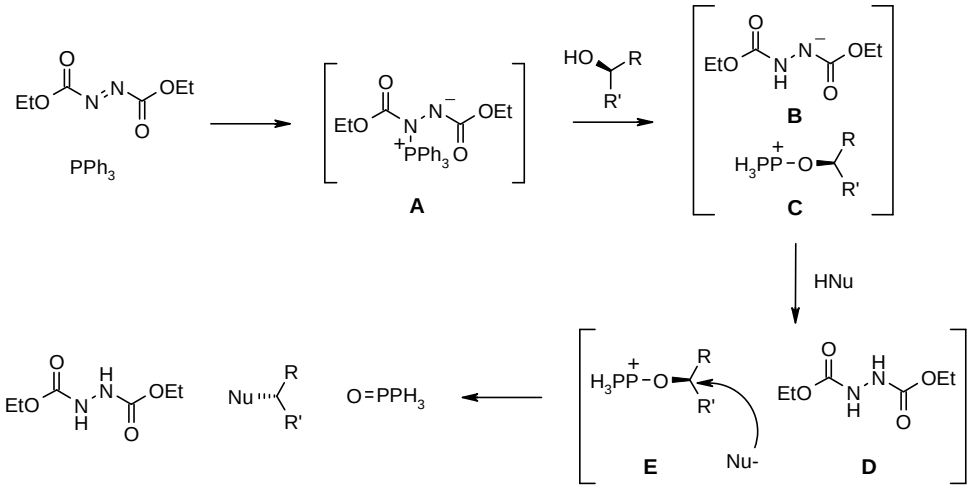


Figure 7: Mechanism of the Mitsunobu reaction.

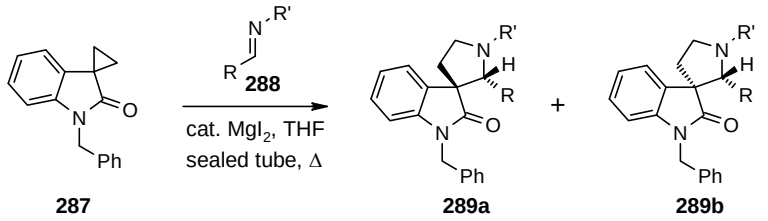
One of the major drawbacks to the Mitsunobu reaction is the requirement for stoichiometric quantities of DEAD and PPH_3 that each produces a by-product. Thus even in high yielding reactions the desired product can often be difficult to isolate from the reaction mixture. Much research has been directed towards developing alternatives to DEAD and PPH_3 that facilitate isolation of the coupled product.[56] An additional constraint of the reaction is the requirement of a nucleophilic coupling partner with a p*K*a of below 13, preferably below 11. If the p*K*a of the coupling partner is over 11, side reactions can lead to undesired products. Alternative reagents that moderate the limitations of p*K*a and extend the scope of the reaction are also being sought.[56]

A range of conditions were examined in the hope of promoting the desired intermolecular Mitsunobu reaction but to no avail. In each case the intramolecular cyclisation to **285** outpaced the desired coupling reaction to **278**. We also explored the opening of cyclopropane **285** with various nucleophiles. Our only success came using the forcing conditions of HBr in acetic acid, which gave the bromide **286** in modest yield. To our frustration, attempts to displace the bromide with various nucleophiles resulted in ring closure to cyclopropane **285**.

Cyclopropane ring expansion-a route towards the ABDE ring system

At this juncture our attention turned to a recent publication by Carreira and coworkers, who had successfully induced the expansion of activated cyclopropanes with imines to saturated 5 membered ring nitrogen heterocycles.[57] The reaction used

MgI_2 as a bifunctional catalyst, combining the Lewis acidity of the metal centre (Mg^{II}) with nucleophilicity in the counterion (I^-) (Scheme 60).



Scheme 60: Carreira's ring expansion strategy.[57]

Carreira *et al*. found that cyclopropane **287** could be smoothly transformed into the ring expanded tricycles **289** (as a mixture of diastereoisomers) on heating with an imine in the presence of 5 mol% MgI_2. Stereoselectivity was dependent on the substituted imine partner **288** and on the *N*-protecting group of the oxindole **287**. The major isomer isolated in the majority of cases, had the correct stereochemistry for the *Aspidosperma* alkaloids. Carreira proposed three possible mechanistic pathways for the reaction which differ in the sequence of events leading to C-N and C-C bond formation.[57] In pathway A, the imine acts directly as the nucleophile to open the cyclopropyl ring in **287**. The resulting iminium ion **290** then undergoes ring closure giving **289**. In pathway B, ring opening is induced by iodide to provide enolate **291**. *N*-alkylation of the imine follows to give **290** and then **289**. In pathway C, enolate **291** is first captured by the imine to give **292**, to set up an alkylative cyclisation to **289** (Figure 8).

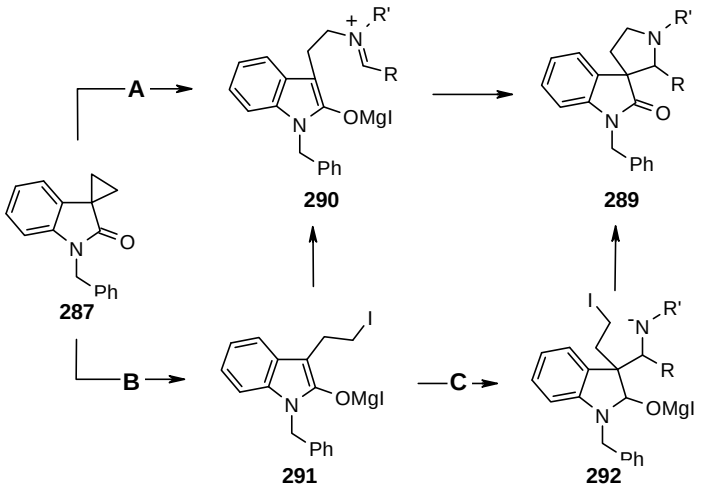
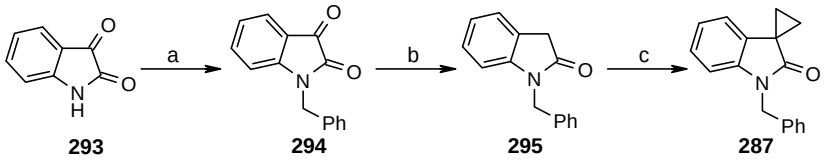


Figure 8: Carreira's potential mechanistic pathways leading to ring expansion.[57]

The observation that the halide counterion played a critical role in the reaction (no reaction was observed with $Mg(OTf)_2$) led Carreira to conclude that iodide **291** was indeed a likely intermediate.

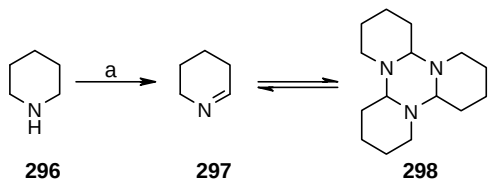
This chemistry seemed ideally suited for construction of the ABDE ring system of aspidospermidine as the requisite cyclopropane **287** was easily prepared on a multi-gram scale (Scheme 61). Thus, *N*-benzylation of isatin **293** was followed by a Wolff-Kishner style reduction of the C3 ketone to **295**. The Na-enolate of **295** then underwent a clean alkylative cyclisation with 1,2-dibromoethane to afford cyclopropane **287**.



Scheme 61: Synthetic route towards cyclopropane **287**.

Reagents and conditions: (a) NaH, BnBr, DMF, RT, 1 h, 91%; (b) $NH_2NH_2.H_2O$, Δ, 16 h, 99%; (c) NaH, DMF, $BrCH_2CH_2Br$, RT, 16 h, 67%.

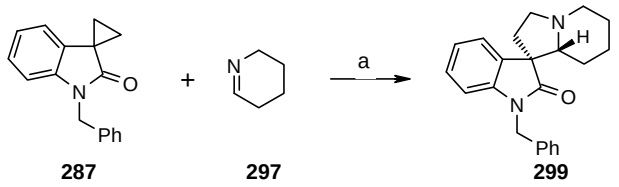
Construction of the ABDE ring system of aspidospermidine next required us to prepare a cyclic imine. In the first instance we decided to examine a model system as the unsubstituted cyclic imine **297** is a literature compound available through oxidation of piperidine **296**.[58] Thus, *N*-chlorination of piperidine with calcium hypochlorite led to the *in situ* formation of *N*-chloropiperidine, which underwent smooth dehydrochlorination with alcoholic potassium hydroxide to yield imine **297** as the polycyclic trimer **298** (Scheme 62).



Scheme 62: Synthesis of imine **297**.

Reagents and conditions: (a) (1) $Ca(OCl)_2$, MTBE, AcOH, H_2O, -10°C. (2) KOH, MeOH, MTBE, RT, 16 h, 17%.

With imine **297** and cyclopropane **287** in hand, our attention focused on the key ring expansion protocol. Pleasingly, heating a THF solution of cyclopropane **287**, imine **297** and MgI_2 to 125 °C under microwave irradiation gave the desired tetracycle **299** in 70% yield (Scheme 63). The sealed tube conditions described by Carriera[57] were not successful in our hands. Initially the reaction proved highly capricious which we attributed to the need for rigorously anhydrous conditions. However, further experimentation showed that imine purity was of far greater importance, as with freshly recrystallised imine trimer **298** the reaction worked consistently well even with 'aged' catalyst.

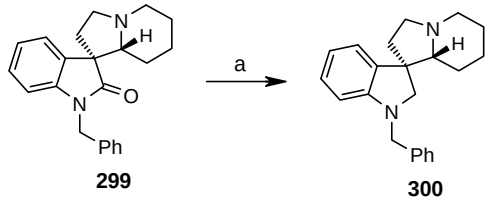


Scheme 63: Ring expansion towards the ABDE ring system.

Reagents and conditions: (a) MgI_2, THF, 125 °C, 5 h, microwave, 70%.

The reaction was examined in a range of solvents, at various temperatures, catalyst loading and substrate stoichiometries. The use of dioxane as a reaction solvent allowed us to increase the reaction temperature to 140 °C, though this afforded no apparent benefit. Best yields were attained when a THF solution of **287** (1 equiv.), **297** (1 equiv.) and MgI_2 (1 equiv.) were heated in a microwave at 125 °C for 5 h.

With the model tetracyclic ABDE system realized and the ring expansion reaction understood we looked at reduction of the oxindole centre. For the key radical cyclisation step to occur in the natural product system the C2 position of the indoline ring needs to be unmasked to allow for radical translocation by 1,5-H atom abstraction. The model ABDE system **299** gave us the opportunity to test the reduction of this centre. Pleasingly treatment of a THF solution of oxindole **299** with $LiAlH_4$ at 70 °C for 2 h afforded indoline **300** in 79% yield (Scheme 64).



Scheme 64: Oxindole reduction.

Reagents and conditions: (a) $LiAlH_4$ (1.0 M in THF), THF, 70 °C, 2 h, 79%.

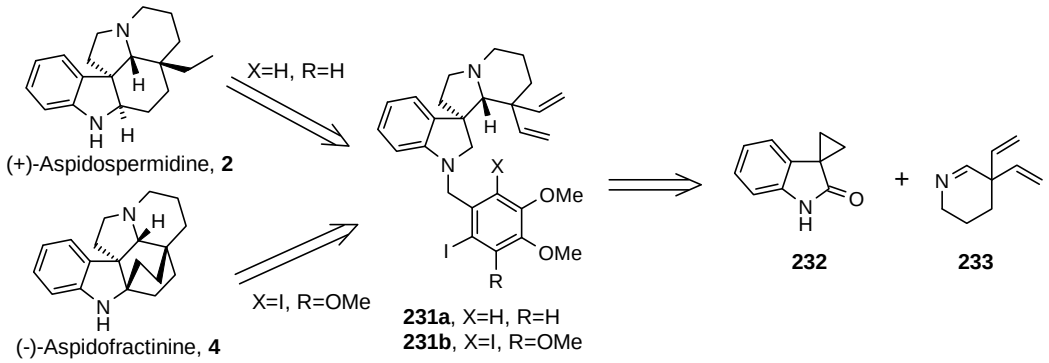
Conclusions

Early investigations into the preparation of the indoline core were beset with significant problems. Switching to an oxindole base starting material facilitated elaboration of the C3 centre and installation of a cyclopropane moiety. Ring expansion of cyclopropane **287** with imine **297** provided a quick and efficient route to the ABDE ring system of the *Aspidosperma* alkaloids. Subsequent reduction of the oxindole unmasked C2 in indoline **300**, completing work on this model for the natural product ring system.

Chapter 3 – Towards Aspidospermidine and Aspidofractinine

Required divinyl imine

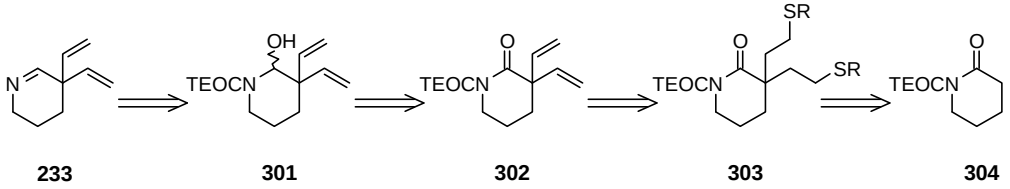
With a route to the ABDE ring system realized, attention turned to our natural product targets. For the proposed radical translocation chemistry to proceed, *viz*. **231a→2** and **231b→4**, we needed to introduce two vinyl substituents at C3 of the cyclic imine (*i.e.* **233**) (Scheme 62). With no literature method reported, we set about the task of developing an approach to this seemingly trivial target.



Scheme 65: Retrosynthesis of our proposed approach to aspidospermidine **2** and aspidofractinine **4**.

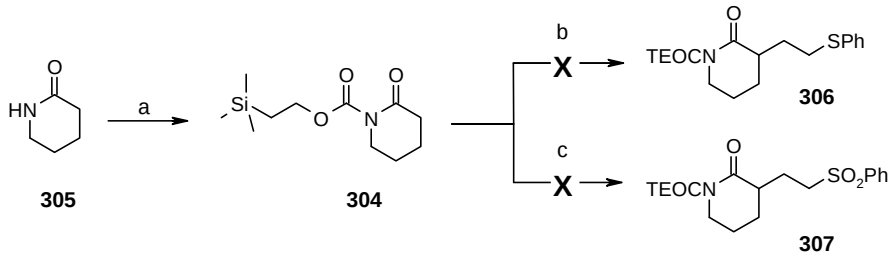
Early routes towards divinyl imine 233

Our first approach drew inspiration from the work of Grieco and coworkers who prepared α-substituted cyclic imines from lactams by a method akin to that shown in Scheme 66.[59] Our plan was to introduce the vinyl groups using a double alkylation of TEOC-protected δ-valerolactam **304** to **303**. Oxidation and thermally induced elimination should then reveal divinyl lactam **302**. Reduction of the amide and fluoride-induced elimination then gives imine **233** (Scheme 66).



Scheme 66: Retrosynthesis of our first approach to divinyl imine **233**.

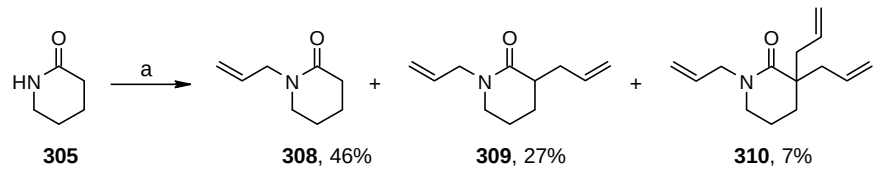
The approach proved troublesome from the outset with TEOC protection of **305** proceeding poorly in 23% yield. Our attempts to introduce the requisite sulfide containing side chains, *viz*. **304** to **306** or **307**, proved equally fruitless with no products derived from α-alkylation of the enolate being observed (Scheme 67).



Scheme 67: Alkylation of TEOC-protected δ-valerolactam **304**.

Reagents and conditions: (a) LiHMDS, THF, -78 °C, 30 min then 2-(trimethylsilyl)ethyl 4-nitrophenylcarbonate, -78 °C to RT, 16 h, 23%; (b) LDA, THF, -78 °C, $PhSCH_2CH_2Cl$; (c) LDA, THF, -78 °C to RT, phenyl vinyl sulfone.

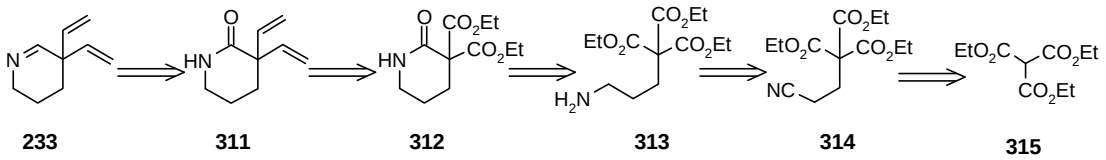
With the introduction of the sulfur-containing side-chains proving problematic, a less direct method of introducing two vinyl groups at C3 was examined. Our idea centered on the use of allyl bromide as the electrophilic partner in the enolate alkylation reactions. This would facilitate the introduction of two allyl groups at C3 which could be transformed into the required vinyl groups by an array of protocols. Here too, the approach was thwarted at an early stage, as we were unable to control the allylation reaction. In a typical reaction the major isolated product was that derived from *mono*-allylation at nitrogen, **308** (46%). In addition, both the *bis*-allylated and *tris*-allylated products, **309** (27%) and **310** (7%) respectively, were formed in low yield (Scheme 68). Reaction optimization proved ineffective with low yields of the required product **310** obtained on each occasion.



Scheme 68: Alkylation of δ-valerolactam **305**.

Reagents and conditions: (a) *n*-BuLi, TMSCl, THF, -78 °C to 0 °C, 3 h, then LDA, allyl bromide, THF, -78 °C to RT, 16 h.

Our attention next focused on a reported synthesis of lactam **312** by Michael and coworkers,[60] as we hoped that the two esters could be manipulated to form the requisite 3,3-divinyl substituents (Scheme 69).

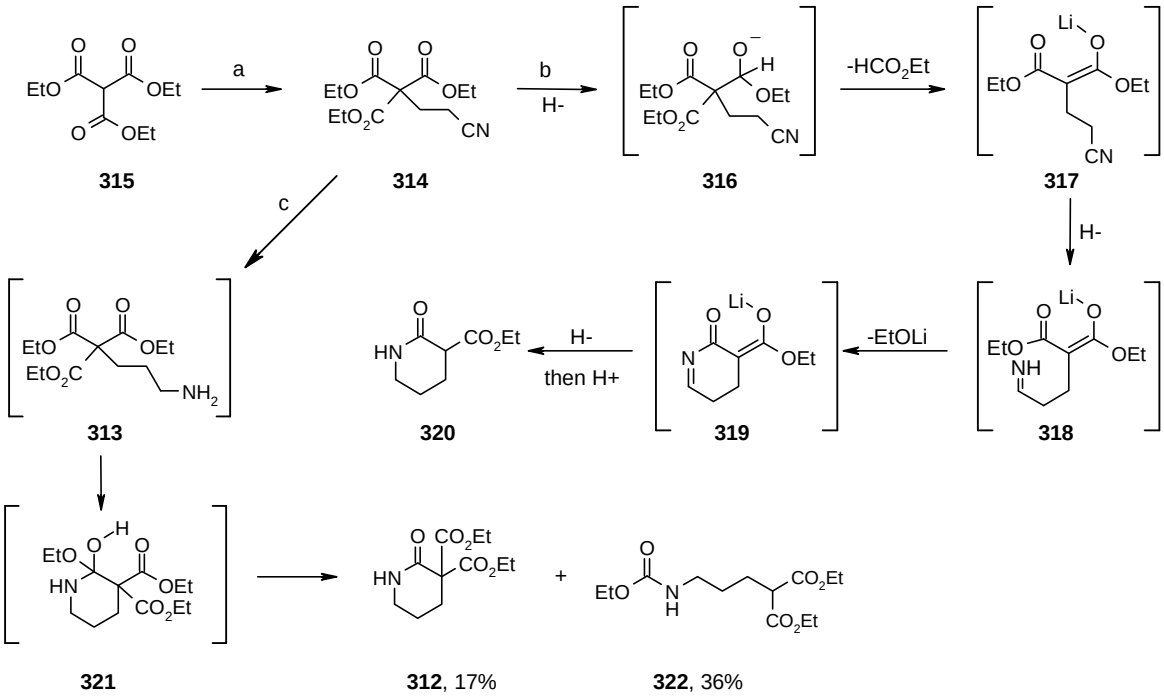


233 **311** **312** **313** **314** **315**

Scheme 69: Retrosynthesis of our second approach to divinyl imine **233**.

Nitrile **314** was prepared according to Michael's procedure[60] from triethyl methanetricarboxylate **315** and acrylonitrile. Harsh hydrogenation conditions (Raney Ni, high pressures) were reported for the reduction of nitrile **314** to amine **313**, so alternative conditions were sought to achieve this conversion (Scheme 70). Pleasingly, chemoselective reduction of the nitrile was achieved by reduction of a THF solution of **314** with $LiAlH_4$ at RT for 24 h, followed by heating at reflux for 1 h. However, the product given was lactam **320**, lacking one of the ester functions at C3. This suggests that the hydride initially adds to one of the ester moieties. The resultant alkoxide **316** next collapses to enolate **317** with ejection of ethyl formate. Reduction of the nitrile follows, with cyclisation, to give **320** on workup.

With hydride additions proving problematic, hydrogenation conditions were explored using less forcing conditions than those performed by Michael. Hydrogenation of nitrile **314** was achieved using Adams' catalyst (PtO_2) and hydrogen at RT and atmospheric pressure resulting in three products. These were the desired lactam **312** (17%), the rearranged malonate **322** (36%) and unidentified dimeric material. The major products **312** and **322** arise from nucleophilic attack of the intermediate amine **313** on one of the ester functionalities. The thus formed tetrahedral intermediate **321** may then collapse with ejection of ethanol to provide lactam **312**. Alternatively, ejection of the malonate leads to ring scission and the formation of **322** (Scheme 70).

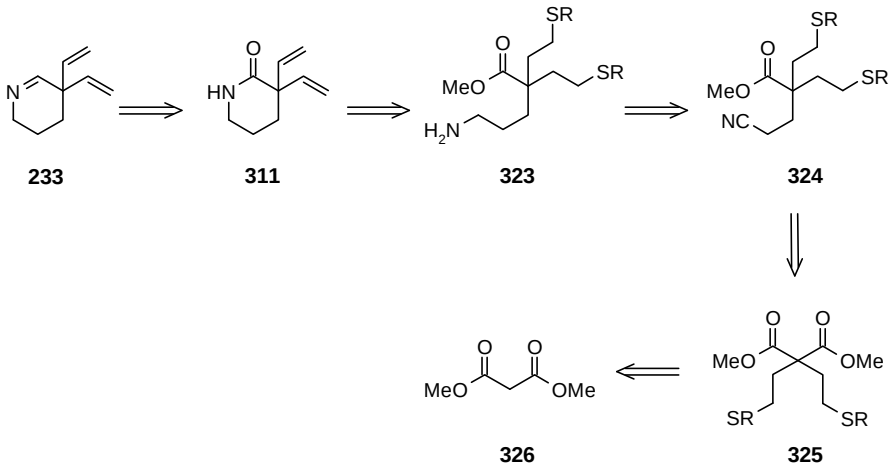


Scheme 70: Tri-ester pathway towards lactam **312**.

Reagents and conditions: (a) acrylonitrile, Bu_4NHSO_4, K_2CO_3, PhMe, RT, 72 h, 46%; (b) $LiAlH_4$ (1.0 M in THF), THF, RT, 24 h, Δ, 1 h, 80%; (c) PtO_2, H_2, EtOH, RT, 16 h.

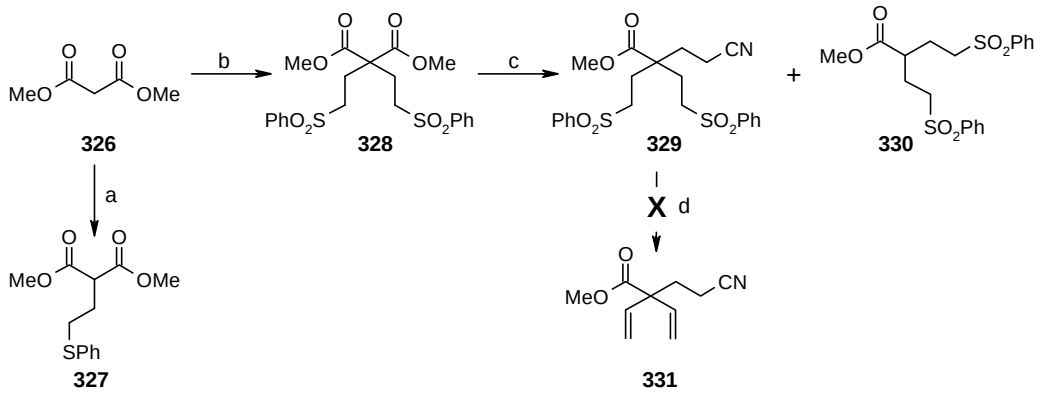
A return to sulfur: route towards divinyl imine 233

A solution to our problem was finally realized using the strategy outlined in Scheme 71. The plan sought to take dimethyl malonate **326** and introduce two sulfide-containing side-chains as precursors to the 3,3-divinyl moiety **325**. Decarboxylation of **325** followed by trapping of the resultant anion with acrylonitrile introduces the required three carbon unit and a masked amine. Reduction of nitrile **324** should then induce cyclisation to lactam **311** which in turn can be transformed to the imine **233**.



Scheme 71: Retrosynthesis of our third approach to divinyl imine **233**.

Alkylation of dimethyl malonate **326** with 2-chloroethyl phenyl sulfide gave the *mono*-addition product **327** (36%) and traces of decarboxylated material. Double addition could not be achieved with this electrophile, but was readily accomplished using phenyl vinyl sulfone, providing the known[61] *bis*-sulfone **328** (95%) and trace *mono*-addition product (3%) (Scheme 72).

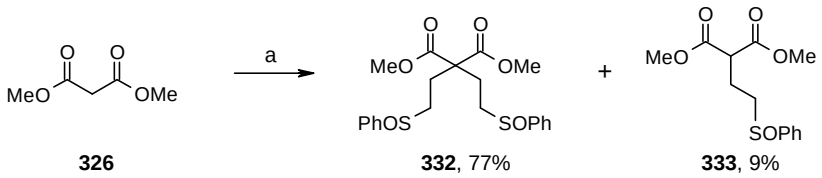


Scheme 72: Sulfides and sulfones.

Reagents and conditions: (a) NaH, DMF, RT, 30 min, then $PhSCH_2CH_2Cl$, 60 °C, 16 h, 36%; (b) Phenyl vinyl sulfone, $[RuH_2(PPh_3)_4]$, MeCN, RT, 4 d, 95%; (c) acrylonitrile, NaI, DMF, Δ, 16 h; (d) DMF, Δ, 24 h or DMF, microwave, 2 h.

With the *bis*-alkylated material in hand the decarboxylation-addition protocol was attempted. A solution of **328**, acrylonitrile and NaI was heated at 130 °C for 16 h to give an inseparable mixture of desired product **329** (major) and decarboxylated material **330** (minor). Attempted thermal elimination of the sulfones met with failure when heating at reflux in DMF or at 200 °C under microwave irradiation. We concluded that the sulfone moiety was too stable (with no degradation seen) to undergo elimination and that a switch to the corresponding sulfoxide would be beneficial.

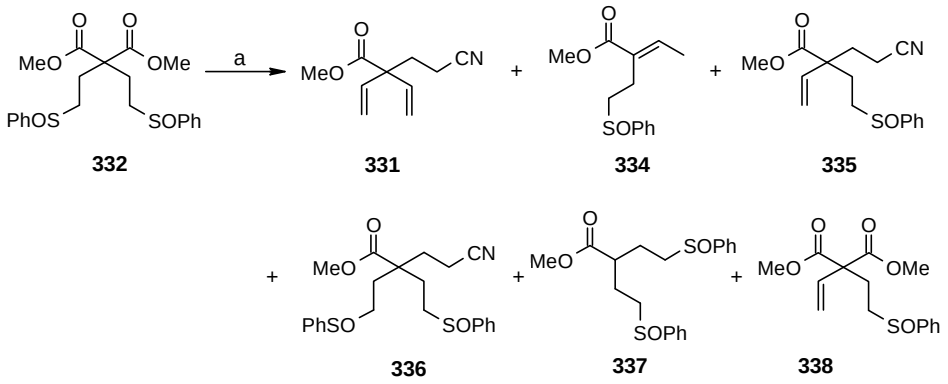
Phenyl vinyl sulfoxide was thus used, along with catalytic NaH (0.2 equiv.), to introduce two sulfoxide side chains to form malonate **332** (77%) and the *mono*-addition product **333** (9%) (Scheme 73). Use of a full equivalent of NaH diminished the yield significantly through formation of polymerized products.



Scheme 73: Exchange to sulfoxides.

Reagents and conditions: (a) NaH (0.2 e.q.), DMF, phenyl vinyl sulfoxide, RT, 48 h.

With *bis*-sulfoxide **332** in hand, we next examined the decarboxylation-addition sequence. Heating *bis*-sulfoxide **332**, acrylonitrile and NaI in DMF to 130 °C for 16 h produced a complex product mixture comprised of the desired material **336**, decarboxylation product **337** and lesser amounts of the sulfoxide elimination products **331**, **334**, **335** and **338** (Scheme 74).

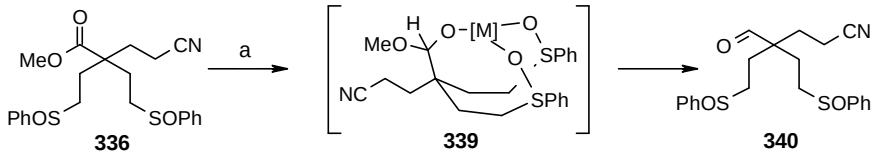


Scheme 74: Sulfoxide elimination issues.

Reagents and conditions: (a) NaI, acrylonitrile, DMF, 130 °C, 16 h.

The extent to which each of these products were produced was strongly influenced by reaction temperature and time. Higher reaction temperatures (>140 °C) and prolonged reaction times (> 12 h) produced more of the elimination products **331** (10%) and **335** (10%). However, in general these reactions were less efficient and gave products of lower purity. Limiting the temperature to 130 °C and the reaction time to 10 h, produced cleaner reactions, with higher overall yields for the usual isolated products **336** (65%) and **335** (20%). These could each be transformed into **331** in high yield by thermolysis (Scheme 76), the two-step process being superior to all the 'one-pot' procedures investigated.

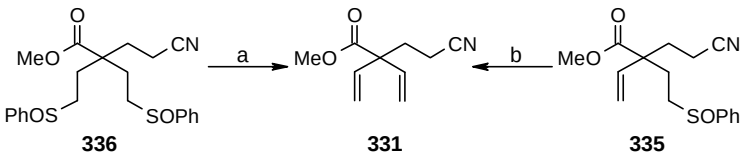
Reduction of the nitrile functionality in **336** was explored in the hope that the resulting amine would undergo spontaneous cyclisation to the vicinal ester to produce the lactam core. Hydrogenation was investigated as a means to reduce the nitrile moiety of **336** but with no success. A range of catalysts, loadings and temperatures were examined using hydrogen at atmospheric pressure, but no sign of reaction was observed. Reduction with $LiAlH_4$ at -78 °C unexpectedly gave aldehyde **340** in 56% yield (Scheme 75). We suspect that the neighboring sulfoxide groups stabilize the tetrahedral intermediate **339** preventing its collapse *in situ* and further reduction to the alcohol.



Scheme 75

Reagents and conditions: (a) $LiAlH_4$ (1.0 M in THF), THF, -78 °C, 2 h, 56%.

With the sulfoxide functionality proving troublesome for the required nitrile reduction, we decided to re-order the reaction sequence and conduct the sulfoxide elimination at an earlier stage. Thermally induced elimination was achieved by heating *bis*-sulfoxide **336** or *mono*-sulfoxide **335** under microwave irradiation at 140-150 °C in DMF (Scheme 76). Classical thermolysis conditions proved an effective alternative, but extended reaction times considerably and produced less pure product.

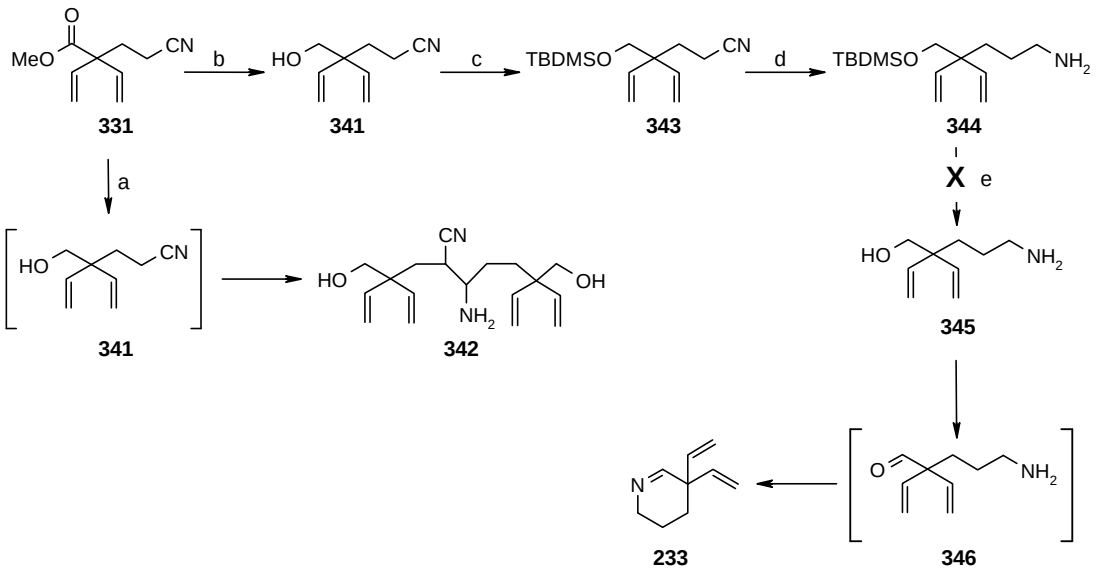


Scheme 76: Thermal elimination of sulfoxides **335** and **336**.

Reagents and conditions: (a) DMF, microwave, 110 W, 150 °C, 2 h, 75%; (b) DMF, microwave, 100 W, 140 °C, 30 min, 64%.

With the divinyl functionality now established in three steps from dimethyl malonate **326**, attention turned to formation of the imine. $LiAlH_4$ reduction of the nitrile and ester moieties in **331** could now be achieved. Using $LiAlH_4$ at -78 °C for

2 h achieved reduction of the ester functionality only. By allowing the reaction to warm to 0 °C for 4 h, we hoped to achieve reduction of both the ester and nitrile groups. Unexpectedly, the product given was aminodiol **342**, along with RSM (Scheme 77). Consequently, we found it necessary to employ a stepwise sequence to achieve our goal of reducing both the ester and nitrile functions. Thus, protection of alcohol **341** as its TBDMS ether produced smoothly silyl ether **343**. Reduction of the nitrile with $LiAlH_4$ at 0 °C then gave amine **344** in an optimized 72% yield. Deprotection to alcohol **345** followed by oxidation (IBX) to the aldehyde **346** should produce the desired imine directly through condensation of the amine and resultant aldehyde. Unfortunately, although we believe that deprotection of silyl ether **344** with TBAF gave amino-alcohol **345**, its high water solubility prevented its isolation or purification. Attempted oxidation (IBX) of the crude alcohol **345** proved unsuccessful.

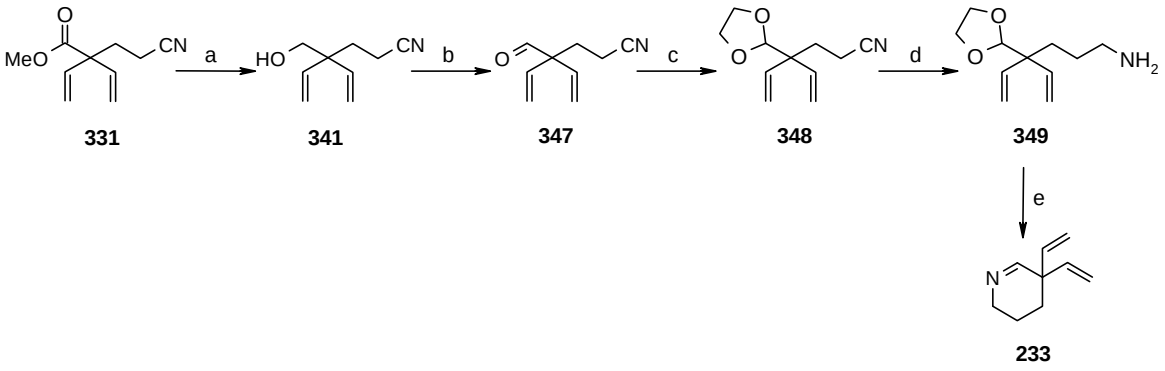


Scheme 77: Functional group manipulation towards imine **233**.

Reagents and conditions: (a) $LiAlH_4$ (1.0 M in THF), THF, -78 °C, 2 h, 0 °C, 4 h, 5%; (b) $LiAlH_4$ (1.0 M in THF), THF, -78 °C, 6 h, 84%; (c) imidazole, TBDMSCl, DMF, RT, 20 h, 65%; (d) $LiAlH_4$ (1.0 M in THF), THF, 0 °C, 5 h, 72%; (e) TBAF (1.0 M in THF), THF, RT, 24 h.

Though the reaction sequence had failed to deliver imine **233**, we believed that a change in the protecting group strategy would allow its preparation. Thus, reduction of ester **331** was accomplished with $LiAlH_4$ at -78 °C then the resultant alcohol **341** was oxidized to aldehyde **347** with Dess-Martin periodinane. Protection

of the aldehyde as acetal **348** then facilitated reduction of the nitrile with $LiAlH_4$ at 60 °C to give amine **349**. Finally deprotection of the acetal was achieved with 10% HCl, inducing spontaneous cyclisation to the desired divinyl imine **233** (Scheme 78). Interestingly, divinyl imine **233** was a stable entity and unlike its unsubstituted analogue **297**, showed no tendency to form a cyclic trimer akin to **298**.

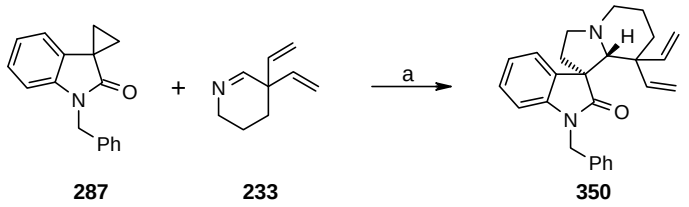


Scheme 78: Functional group manipulation towards imine **233**.

Reagents and conditions: (a) $LiAlH_4$ (1.0 M in THF), THF, -78 °C, 6 h, 84%; (b) Dess-Martin periodinane, $CHCl_3$, RT, 3 h, 95%; (c) ethylene glycol, *p*-TSA (5 mol%), PhMe, Dean-Stark, Δ, 6 h, 98%; (d) $LiAlH_4$ (1.0 M in THF), THF, 60 °C, 4 h, 84%; (e) 10% HCl, RT, 2 h, then 10% NaOH to pH 9, RT, 2 h, 68%.

Ring expansion: towards the targets

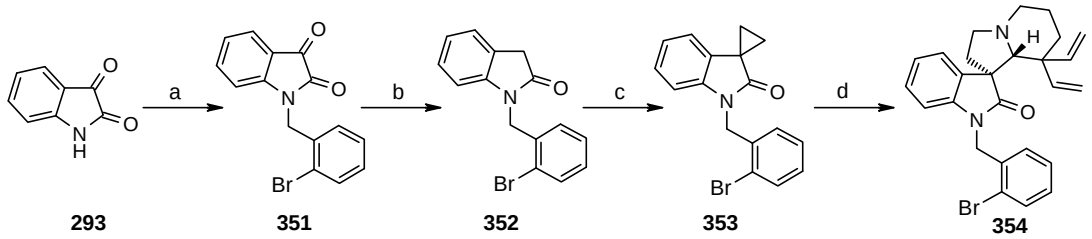
With a reliable synthesis to the divinyl imine **233** realized, attention turned to the cyclopropane ring expansion reaction that had proved successful in our model study. Cyclopropane **287**, divinyl imine **233** and an equivalent of MgI_2, were heated at 125 °C under microwave irradiation in a small scale reaction to give tetracycle **350** in an unoptimised 4% yield along with recovered cyclopropane **287** (64%) (Scheme 79).



Scheme 79: Ring expansion of cyclopropane **287** with imine **233**.

Reagents and conditions: (a) MgI_2, THF, 125 °C, microwave, 3 h, 4% and 64% RSM.

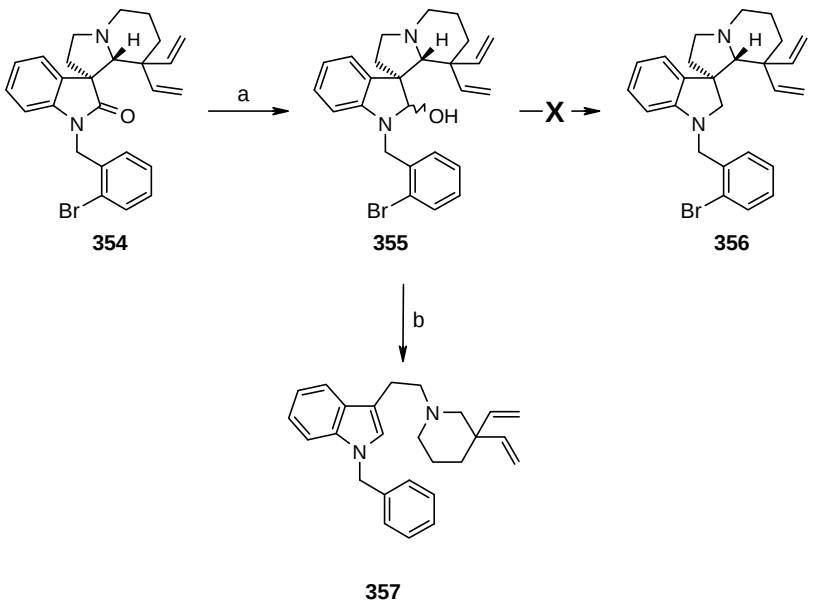
Attention now turned to the synthesis of the more advanced analogue **354** containing an *ortho*-halide in the *N*-benzyl group, as this would allow us to effect the key radical translocation sequence. Thus, isatin **293** was protected with 2-bromobenzyl bromide to give **351**. A Wolff-Kishner reduction to **352** was followed by cyclopropane formation to give **353**. Pleasingly, ring expansion of cyclopropane **353** with divinyl imine **233** provided tetracycle **354** in an unoptimised 44% yield together with recovered starting material (34%) (Scheme 80). Thus, in a short, highly convergent sequence, we had successfully prepared the ABDE ring system of aspidospermidine with the requisite functionality required to initiate C-ring closure through radical translocation and cyclisation to the acceptor alkene.



Scheme 80: Synthetic route towards tetracycle **354**.

Reagents and conditions: (a) 2-bromobenzyl bromide, K_2CO_3, KI, MeCN, RT, 16 h, 98%; (b) $NH_2NH_2.H_2O$, Δ, 24 h, 88%; (c) NaH, DMF, $BrCH_2CH_2Br$, RT, 72 h, 62%; (d) MgI_2, **233**, THF, 125 °C, microwave, 3 h, 44% and 34% RSM.

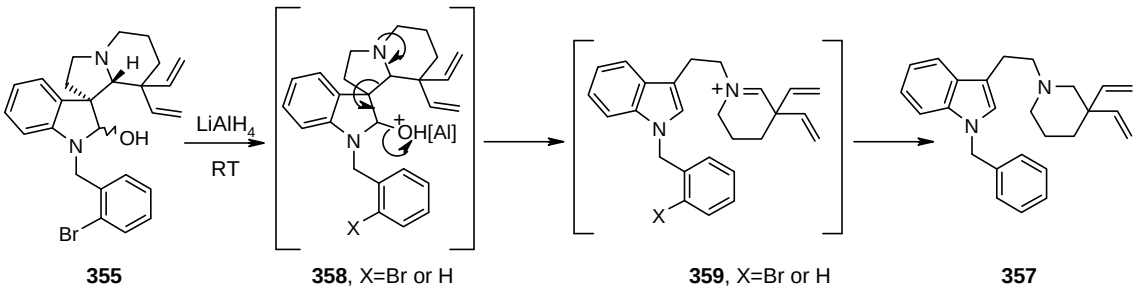
Completion of the total synthesis required reduction of the C2 carbonyl of the oxindole in **354**. Reduction was first examined with $LiAlH_4$ at -78 °C, the low temperature being a precautionary measure to avoid reduction of the aryl bromide. Alas, no reaction was seen at these low temperatures. Warming to 0 °C facilitated consumption of the starting material to a more polar product which was shown to be aminal **355** with the aryl-halide bond still intact. Subjecting **355** to prolonged treatment with $LiAH_4$ at 0 °C failed to induce further reduction, even after 24 h. Allowing the system to warm to RT for 4 h showed complete consumption of intermediate **355** to a less polar product. Unfortunately, the product formed was indole **357** rather than the desired indoline **356** (Scheme 81).



Scheme 81: Reduction of oxindole **354**.

Reagents and conditions: (a) $LiAlH_4$ (1.0 M in THF), THF, 0 °C, 5 h, 45%; (b) $LiAlH_4$ (1.0 M in THF), THF, RT, 4.5 h, 45%.

Formation of **357** is assumed to occur *via* a Lewis acid mediated fragmentation of the E ring (*via* **358**) to form indole **359**. Reduction of the resulting iminium cation **359** and aryl halide then furnishes indole **357** (Scheme 82). That the reduction did not progress in accordance with our model system (**299→300**) is presumed to be due to steric hindrance around the C2 centre. Relief of steric congestion, combined with the need to employ more forcing conditions, presumably contrive to make this unwanted side reaction more favourable.



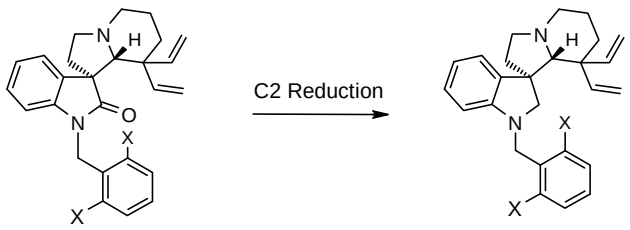
Scheme 82: Fragmentation of ring E.

Unfortunately, time escaped us before alternative reduction conditions and the radical translocation methodologies could be investigated.

Conclusions and future work

In conclusion, robust syntheses of divinyl imine **233** and cyclopropane **353** have been developed. Their union to form the ABDE ring system of aspidospermidine has also been realized using a recently developed ring expansion protocol by Carriera *et al*. Reduction of the oxindole failed to give the desired precursor **356** as seen in the model system (**299→300**).

It should be plausible to achieve the desired reduction of the C2-carbonyl and further investigations are ongoing to establish appropriate reducing conditions (Scheme 83). The ideal situation would leave the carbon-to-halogen bonds intact during the reduction. Results of model studies on the radical translocation methodology are presented in Chapter 4.



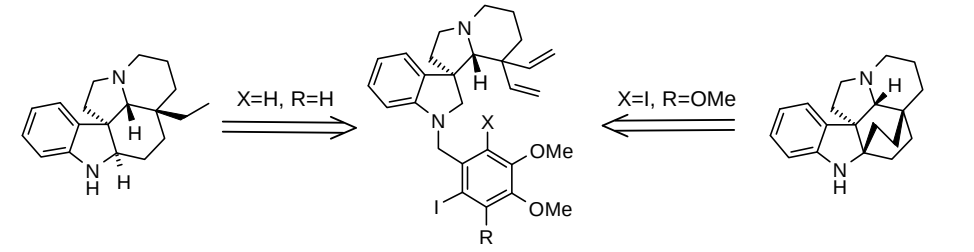
360 **361**

Scheme 83. C2 reduction.

Chapter 4 – Radical Translocation-Cyclisation Methodology

Towards a model system

The second key step in our proposed total syntheses involved a radical translocation and cyclisation cascade. Thus, our plan was to construct the C ring of aspidospermidine **2** from iodide **231a**. Initial homolysis of the C–I bond by treatment of iodide **231a** with Bu_3SnH under standard radical forming conditions, would be followed by translocation of the aryl radical intermediate to C2 of the indoline. A 6-*endo*-trig cyclisation to the proximal alkene then establishes the requisite 6.5.6.6.5 ring system. Similarly aspidofractinine **4** could be achieved from di-iodide **231b**, *via* sequential CH activation at C2 of the indoline to establish its 6.5.6.6.6.5 ring system (Scheme 84).



(+)-Aspidospermidine, **2** — **231a**, X=H, R=H; **231b**, X=I, R=OMe — (-)-Aspidofractinine, **4**

Scheme 84: Radical translocation-cyclisation of key intermediate **231** towards the targets.

The key step relies on a 6-*endo*-trig cyclisation of the C2 indoline radical intermediate to the proximal alkene. At first sight this cyclisation mode may seem counterintuitive with the 5-*exo*-trig cyclisation pathway being more usual. On closer inspection it can be seen that the molecule's rigid molecular framework, owing to the ABDE ring structure, makes it easier to adopt a reactive conformer placing the terminal carbon of the acceptor alkene close to the reactive C2 radical centre (Figure 9).

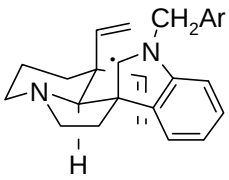
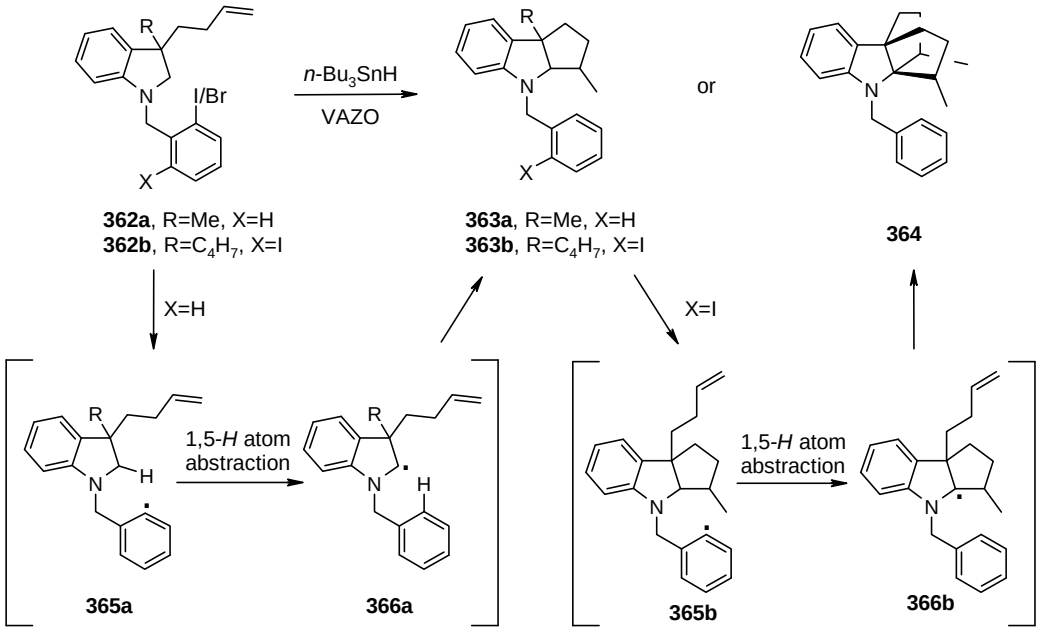


Figure 9: Reactive conformer derived from **231**.

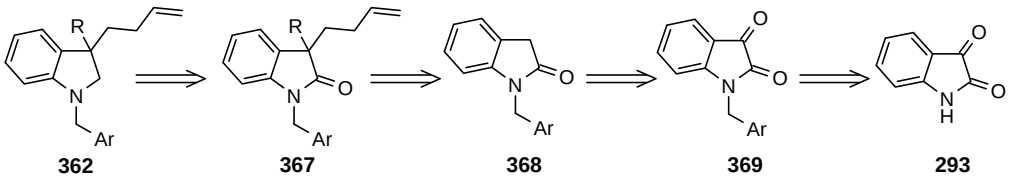
As this key step was to be employed at a very late stage in our synthetic sequence, we decided to investigate some model systems to examine whether this methodology was practicable and efficient. We required a system that would allow us to test the efficiency of intramolecular translocation from the aryl radical to C2 of the indoline by 1,5-*H* atom abstraction. Having achieved this CH activation, we also needed to show that the cyclisation of the indoline radical to a pendant alkene was a facile process (Scheme 85). Importantly, we also wanted to show that by using a 2,6-diiodo benzyl group as a radical primer, CH_2 double activation could be achieved *and* was capable of installing both the C and F rings of aspidofractinine **4** in the one step. Indoline **362** provided the means to examine this chemistry and to investigate the reactivity of the C2 indoline radical intermediate. Lacking the rigid molecular framework of **231**, we anticipated a preference for cyclisation *via* the ubiquitous 5-*exo*-trig cyclisation mode with **362a** yielding **363a** and **362b** yielding propellane **364**.



Scheme 85: Proposed model system.

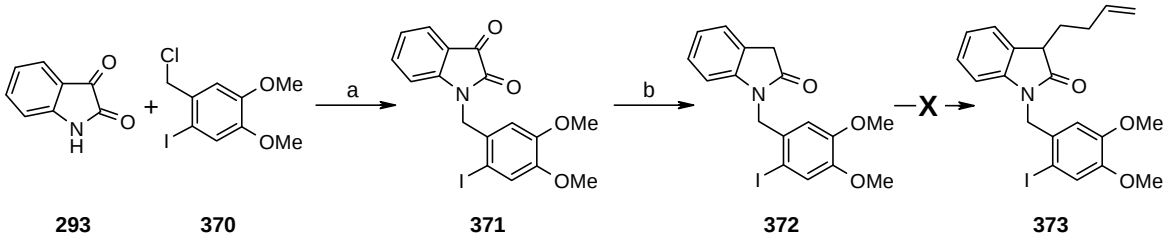
Towards a model system: early approaches

Our retrosynthetic analysis for **362** is outlined in Scheme 86. We hoped that it could be prepared from oxindole **367** *via* reduction of the C2 carbonyl moiety. The C3 side chains could be introduced to **368** *via* sequential alkylation, with *N*-benzylation of isatin **293** providing the means to introduce this key element.



Scheme 86: Retrosynthetic analysis for the model system.

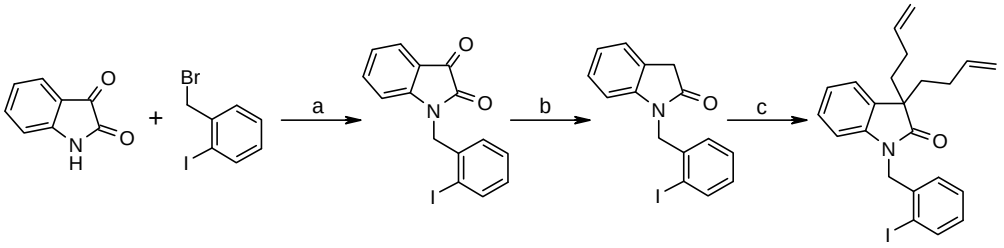
In using isatin **293** as our starting point, we hoped to counter the intractable problem of *N*- vs. *C*-benzylation that had thwarted our early attempts to elaborate oxindole directly. Introduction of the radical primer **370** to isatin **293** proceeded smoothly in 98% yield and a subsequent Wolff-Kishner style reduction of the C3 ketone also proceeded in a pleasing 98% yield to give oxindole **372** (Scheme 87). C3 alkylation of oxindole **372** with 4-bromo-1-butene was then attempted *via* its sodium enolate. Various conditions were attempted without success, with starting material recovered on most occasions along with trace amounts of *O*-alkylation products.



Scheme 87

Reagents and conditions: (a) K_2CO_3, KI, DMF, 50 °C, 6 h, 98%; (b) $NH_2NH_2.H_2O$, Δ, 5 h, 98%, (c) NaH, DMF, 4-bromo-1-butene, RT.

Exchanging the electron rich benzyl moiety **370** for 2-iodobenzyl bromide **374** was easily accomplished and allowed the derivatised oxindole **377** to be prepared in 3 steps from isatin. Alkylation proceeded smoothly in this case to give *bis*-alkylation product **377** in 46% yield together with recovered starting material (Scheme 88).

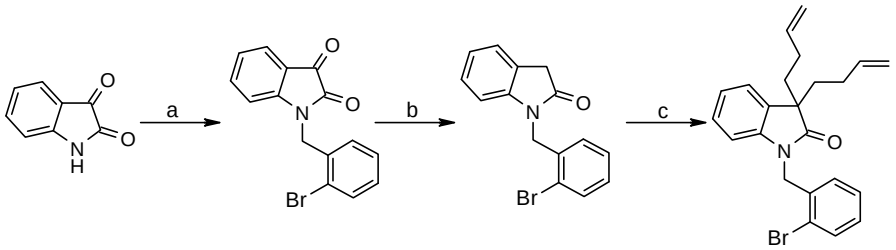


293 **374** **375** **376** **377**

Scheme 88

Reagents and conditions: (a) NaH, DMF, RT, 1 h, 97%; (b) $NH_2NH_2.H_2O$, Δ, 16 h, 68%; (c) 3 equiv. NaH, DMF, 2.5 equiv. 4-bromo-1-butene, RT, 4 h, 46% (and **376**, 30%).

The analogous aryl bromide **378** was also prepared in similar fashion (Scheme 89).

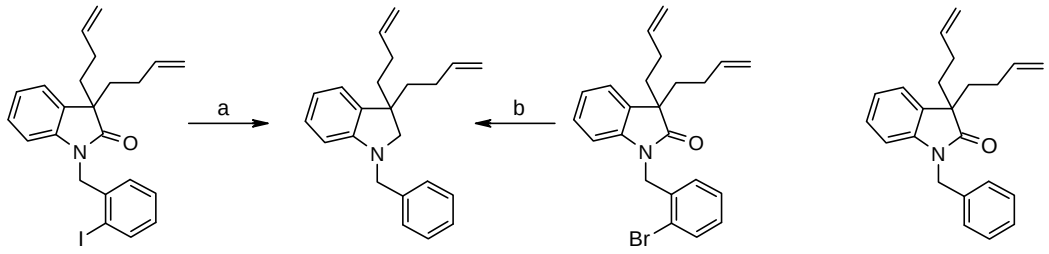


293 **351** **352** **378**

Scheme 89

Reagents and conditions: (a) 2-bromobenzyl bromide, K_2CO_3, KI, MeCN, RT, 16 h, 98%; (b) $NH_2NH_2.H_2O$, Δ, 24 h, 88%; (c) 3 equiv. NaH, DMF, 3 equiv. 4-bromo-1-butene, RT, 4 h, 38%.

To complete the synthesis of the model system we now needed to effect the reduction of oxindoles **377** and **378** to the respective indolines **362**. Attempts to achieve this with $LiAlH_4$ proved intractable as both the oxindole and the carbon-to-halogen bonds in **377** and **378** were reduced to give indoline **379** (Scheme 90).



377 **379** **378** **380**

Scheme 90

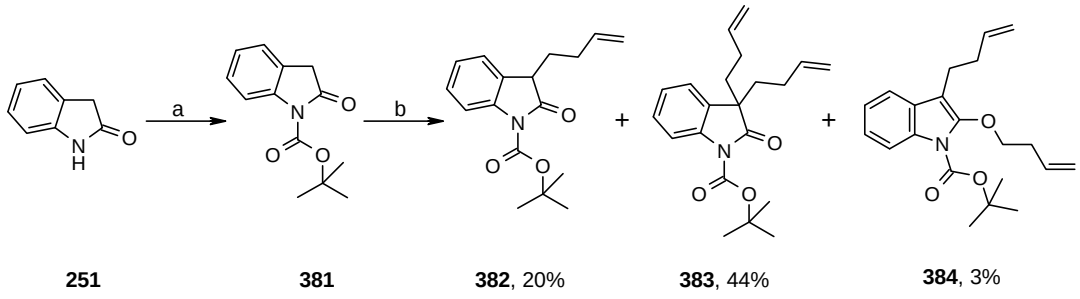
Reagents and conditions: (a) $LiAlH_4$ (1.0 M in THF), THF, Δ, 2 h, 80%; (b) $LiAlH_4$ (1.0 M in THF), THF, RT, 4 h, 40%.

To overcome this difficulty, we sought to effect the reduction of **378** at reduced temperature. Monitoring the reaction by HPLC showed that after 5 hours at 0 °C and 4 hours at RT, significant amounts of starting material remained along with substantial quantities of the over-reduced products **379** and oxindole **380**. Increasing the temperature of reduction led to complete consumption of the starting material but gave only **379** (60%) and **380** (15%) in appreciable quantity. Alternative reducing reagents were investigated including $LiBH_4$, $NaBH_4$ and $Et_2O.BF_3$, and DIBAL-H but each returned the staring material with good mass recovery.

Due to the problems encountered in both the alkylation and reduction steps, it was decided to change the synthetic plan and employ an alternative protecting group for the oxindole nitrogen. In this way we hoped to be able to exploit the aforementioned chemistry to prepare the requisite indoline, then introduce the radical primer group and investigate the radical methodology.

Synthesis of a model system

Oxindole **351** was Boc-protected to **381** in 70% yield. Treatment of **381** with NaH and alkylation with 4-bromo-1-butene proceeded to give *mono*-alkylated oxindole **382** in 20% yield, *bis*-alkylated oxindole **383** in 44% yield, and trace amounts of *O*-alkylated material **384** (3%) (Scheme 91).

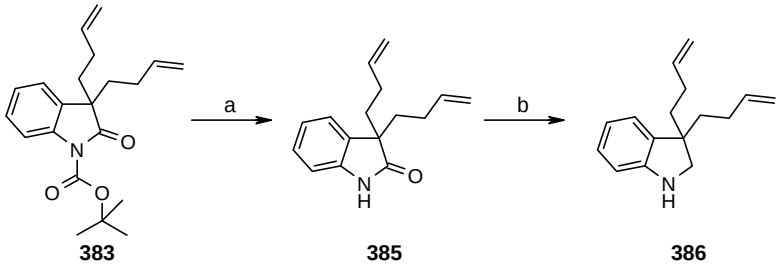


Scheme 91: Boc-oxindole route towards the model system.

Reagents and conditions: (a) Boc_2O, Na_2CO_3, THF, RT, 16 h, 70%; (b) 2.5 equiv. NaH, DMF, 2.5 equiv. 4-bromo-1-butene, RT, 4 h.

The *mono*- and *bis*-alkylated indolines **382** and **383** were both needed for our model study so no attempt was made to optimize the reaction for either product. Deprotection of **383** with TFA in CH_2Cl_2 proceeded smoothly to give oxindole **385**

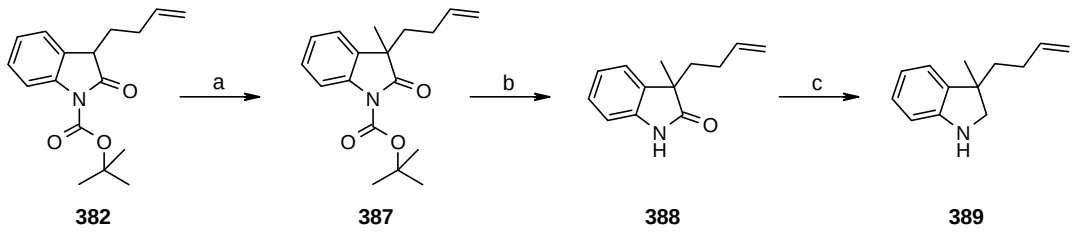
in quantitative yield. Treatment with $LiAlH_4$ then gave indoline **386** in excellent yield (Scheme 92).



Scheme 92: Boc-oxindole route towards the model system.

Reagents and conditions: (a) TFA, CH_2Cl_2, RT, 16 h, 100%; (b) $LiAlH_4$ (1.0 M in THF), THF, 60 °C, 16 h, 88%;

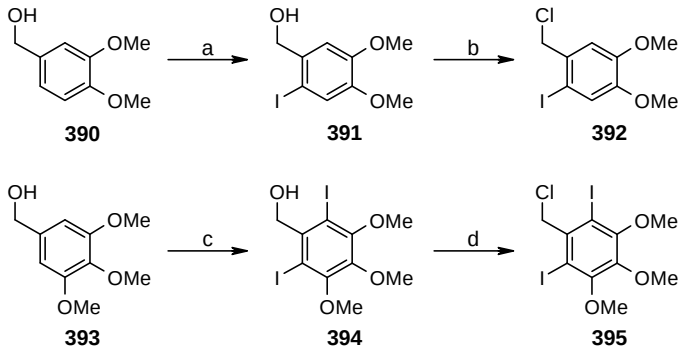
The *mono*-alkylated analogue **382** was first subjected to a second alkylation to replace the C3 hydrogen with a methyl group and hence prevent indole formation in the radical translocation step. Thus, the Na-enolate of **382** was treated with MeI to give **387**, then subjected to the deprotection-reduction sequence to furnish indoline **389** (Scheme 93).



Scheme 93: Boc-oxindole route towards the model system.

Reagents and conditions: (a) NaH, DMF, MeI, RT, 4 h, 41%; (b) TFA, CH_2Cl_2, RT, 16 h, 98%; (c) $LiAlH_4$ (1.0 M in THF), THF, Δ, 20 h, 98%.

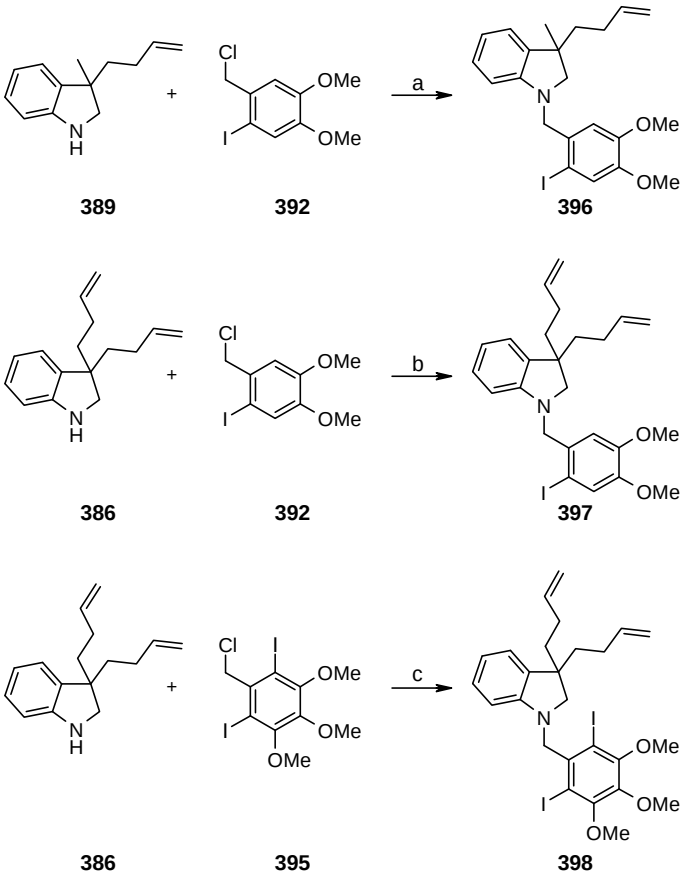
With the indoline analogues in hand, our next task was to prepare the radical primer groups (Scheme 94). Iodination of the electron-rich benzyl alcohols **390** and **393** was achieved in good yield by treatment with iodine and silver trifluoroacetate to give mono-iodide **391** (68%) and di-iodide **394** (99%) respectively. Subsequent treatment of the benzyl alcohols with thionyl chloride then gave the requisite benzyl chlorides **392** (91%) and **395** (100%) in excellent yield.



Scheme 94: Preparation of radical primer groups.

Reagents and conditions: (a) I_2, CF_3COOAg, $CHCl_3$, RT, 1 h, 68%; (b) $SOCl_2$, CH_2Cl_2, RT, 16 h, 91%; (c) 2.5 equiv. I_2, 2.5 equiv. CF_3COOAg, $CHCl_3$, RT, 16 h, 99%; (d) $SOCl_2$, CH_2Cl_2, RT, 16 h, 100%.

The indolines **386** and **389** and radical benzyl primer groups **392** and **395** were now combined to give the three model systems **396**, **397** and **398** (Scheme 95).

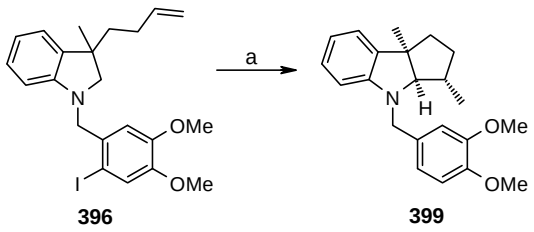


Scheme 95: Coupling indoline core and radical primer groups.

Reagents and conditions: (a) K_2CO_3, acetone, Δ, 16 h, 50%; (b) K_2CO_3, KI, acetone, Δ, 16 h, 79%; (c) K_2CO_3, KI, acetone, Δ, 16 h, 46%.

CH activation and CH_2 double activation of indolines

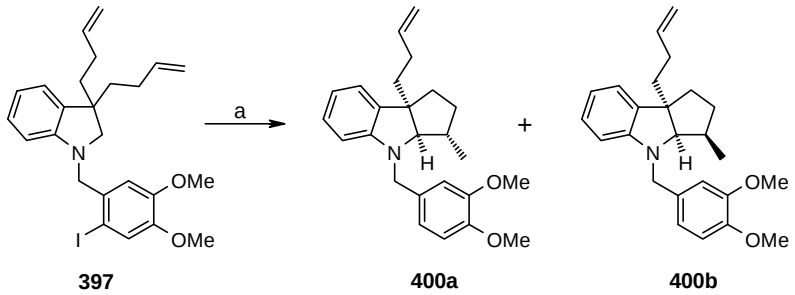
Our investigation of the radical translocation methodology began with model system **396**. Under radical forming conditions, using TTMSS (2.2 equiv.) and 20 mol% VAZO in refluxing toluene for 16 h, we were delighted to find that tricycle **399** was given in 62% yield as a single diastereomer. The result proved that translocation of the aryl radical to C2 of the indoline was both fast and efficient and could be used to induce a subsequent radical cyclisation reaction (Scheme 96).



Scheme 96: Radical translocation and cyclisation.

Reagents and conditions: (a) 2.2 equiv. TTMSS, VAZO (20 mol%), PhMe, 120 °C, 16 h, 62%.

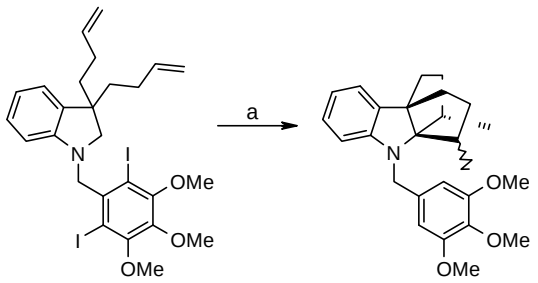
Similarly, treatment of mono-iodide **397** under the radical forming conditions of *n*-Bu_3SnH (2.2 equiv.) and 20 mol% VAZO in refluxing toluene for 16 h smoothly gave tricycles **400** in 76% as an inseparable 6:1 mixture of diastereoisomers (Scheme 97). The switch from TTMSS to *n*-Bu_3SnH as the mediator of the radical reaction was for purely practical reasons. It allowed us to use our potassium carbonate/silica purification methodology (10% K_2CO_3, by weight of silica in stationary phase during column chromatography)[62] to remove tin residues from the product mixture, greatly assisting in the separation of **400** from the by-products of the radical reaction.



Scheme 97: Radical translocation and cyclisation.

Reagents and conditions:(a) 2.2 equiv. *n*-Bu_3SnH, VAZO (20 mol%), PhMe, 120 °C, 16 h, 76%, d.r.6:1.

A more striking result was achieved when di-iodide **398** was treated under the radical forming conditions of *n*-Bu_3SnH (4.4 equiv.) and 20 mol% VAZO in refluxing toluene for 16 h. In this case propellane **401** was isolated as a 1:1 mixture of diastereoisomers in an excellent 90% yield (following K_2CO_3/silica column chromatography). Sequential C-I bond homolysis led to successive translocation of the radical centers to achieve an efficient CH_2 double activation of the C2 indoline centre (Scheme 98)!



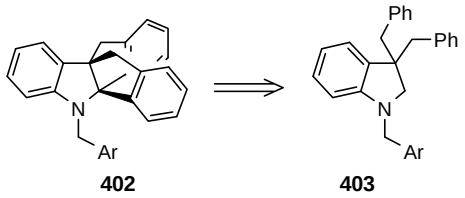
398 **401**

Scheme 98: Radical translocation and cyclisation towards a propellane system.
Reagents and conditions: (a) 4.4 equiv. *n*-Bu_3SnH, VAZO (20 mol%), PhMe, 120 °C, 16 h, 90%, d.r. 1:1.

The three results highlight the potential of radical translocation as a means for derivatisation of centres generally thought of as unactivated. The radical methodology employs a CH bond to effect a ring closure and, more remarkably, CH_2 double activation to construct the propellane ring system from an indoline moiety. These successes show how the radical translocation-cyclisation methodology offers great prospects for achieving a unified approach to our natural product targets.

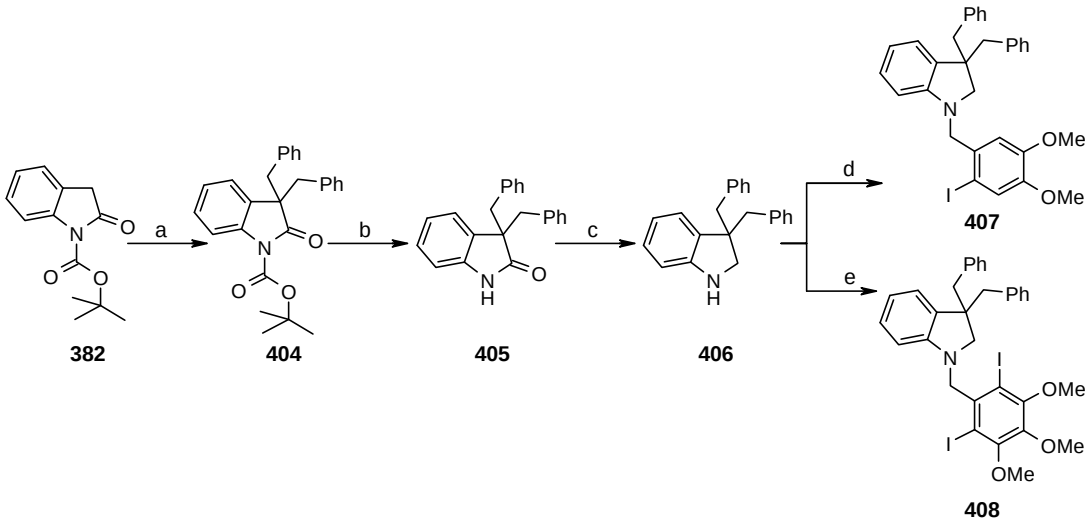
Towards other propellanes

With the positive results obtained from the primary model systems we were encouraged to investigate the scope of the reaction further by looking at related approaches to propellane formation. We envisaged the possibility of cyclisation of a C2 indoline radical intermediate to benzyl substituents at C3 *via* a 5-*exo*/*endo*-trig cyclisation mode. Using a 2,6-diiodobenzyl group at N1 as a radical primer, the tandem cyclisation methodology would give access to propellanes of the type **402** (Scheme 99).



Scheme 99: Towards other propellanes.

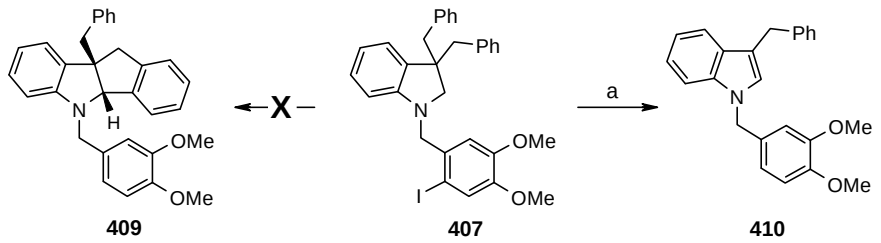
The new system was prepared according to our previously established synthetic route. Thus, Boc-protection of oxindole **251** furnished **382**, which was twice alkylated at C3 using NaH and benzyl bromide to give **404**. *N*-Deprotection (to **405**) followed by $LiAlH_4$ reduction provided indoline **406**. Its coupling with benzyl chlorides **392** and **395** supplied the required precursors **407** and **408** respectively in good yields (Scheme 100).



Scheme 100: Synthesis of a second system.

Reagents and conditions: (a) NaH (2.5 equiv.), DMF, benzyl bromide (2.5 equiv.), RT, 16 h, 60%; (b) TFA, CH_2Cl_2, RT, 4 h, 90%; (c) $LiAlH_4$ (1.0 M in THF), THF, 60 °C, 16 h, 60%; (d) K_2CO_3, KI, **392**, acetone, Δ, 16 h, 76%; (e) K_2CO_3, KI, **395**, acetone, Δ, 16 h, 83%.

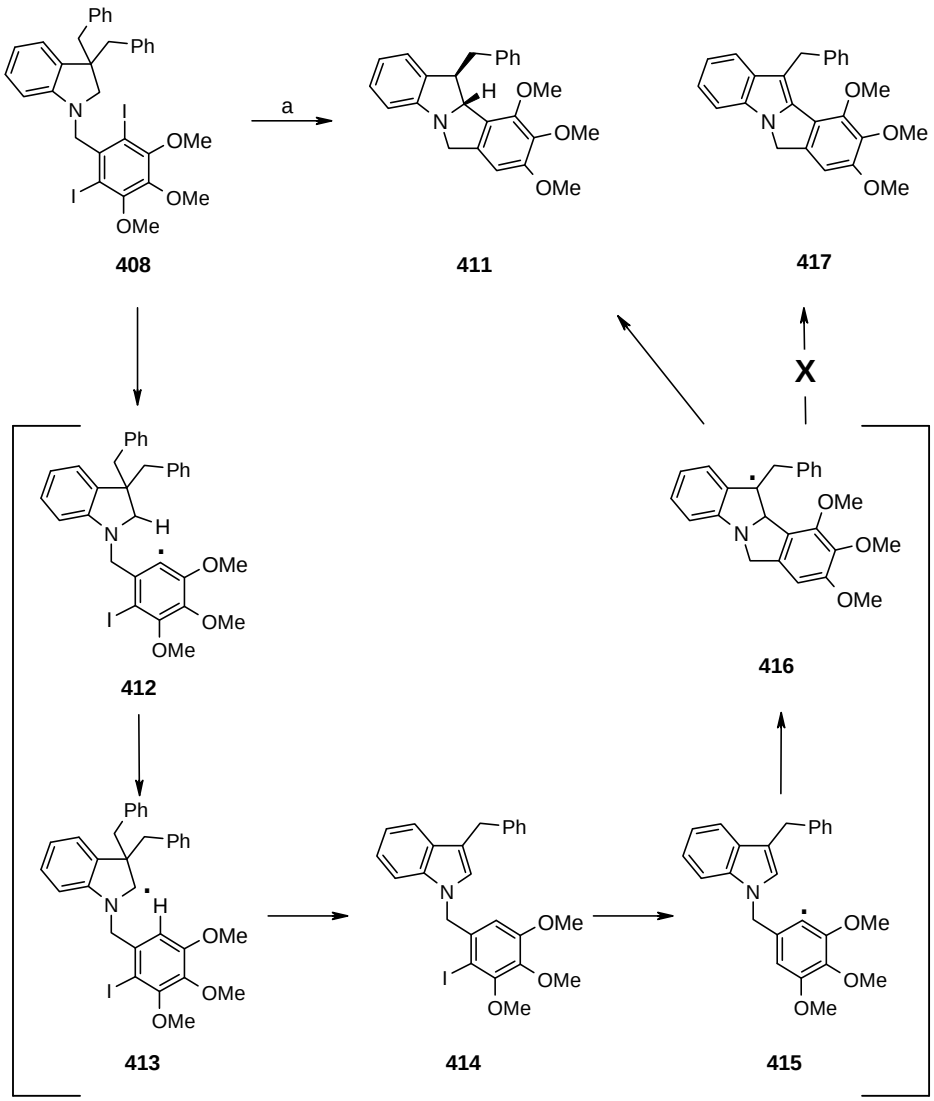
Treatment of mono-iodide **407** under radical forming conditions (*n*-Bu_3SnH, VAZO) failed to induce the anticipated cyclisation to **409** producing instead indole **410** in 95% yield (Scheme 101). This implies that a successful radical translocation to C2 was followed by loss of a stabilised benzyl radical and that this outpaced radical cyclisation to one of the proximal arenes.



Scheme 101: Radical translocation and elimination.

Reagents and conditions: (a) *n*-Bu_3SnH (2.2 equiv.), VAZO (20 mol%), PhMe, 120 °C, 16 h, 95%.

Mindful of this result, we now expected treatment of di-iodide **408** under radical forming conditions to furnish tetracycle **411** rather than propellane **402** (Scheme 102). The first radical translocation to C2 would be expected to form, after loss of a benzyl radical, indole **414**. Homolysis of the second C-I bond would then give aryl radical **415**, setting up a 5-*exo*-trig radical cyclisation to C2 of the indole giving tetracycle **411**.[63]



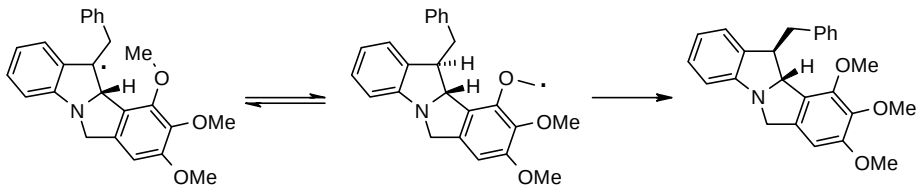
Scheme 102

Reagents and conditions: (a) *n*-Bu_3SnH (4.4 equiv.), VAZO (20 mol%), PhMe, 120 °C, 16 h, 60%.

Pleasingly, when the reaction was conducted using 4.4 equivalents of Bu_3SnH and 20 mol% VAZO in refluxing toluene, **411** was given in 60% yield. NOE experiments confirmed the stereochemical assignment of **411**. Irradiation of the proton at C3 (5.06 ppm), intensified the proton signals for the phenyl ring (7.42-7.34 ppm, 5H), OMe (3.70 ppm, 3H) and most importantly the CH_2Ph group (3.16 and 3.07 ppm, 1H and 1H). On irradiation of the C**H**CH_2Ph proton no significant enhancement was seen in the proton region below 6 ppm.

It is interesting to note that rearomatisation of benzyl radical **416** to indole **417** does not occur. Instead *H*-atom abstraction completes the reaction sequence to give indoline **411**. It is interesting to note the radical at C3 cannot align with the C-H

bond at C2 in this case, which would be required for aromatization through loss of H˙. It is also plausible that H-atom abstraction from one of the proximal aryl methyl ethers, **416→418**, is facile and that this prevents aromatization to the indole. This would also explain the stereochemical outcome, in which a hydrogen atom is delivered to the more encumbered concave face of **418** (Scheme 103).

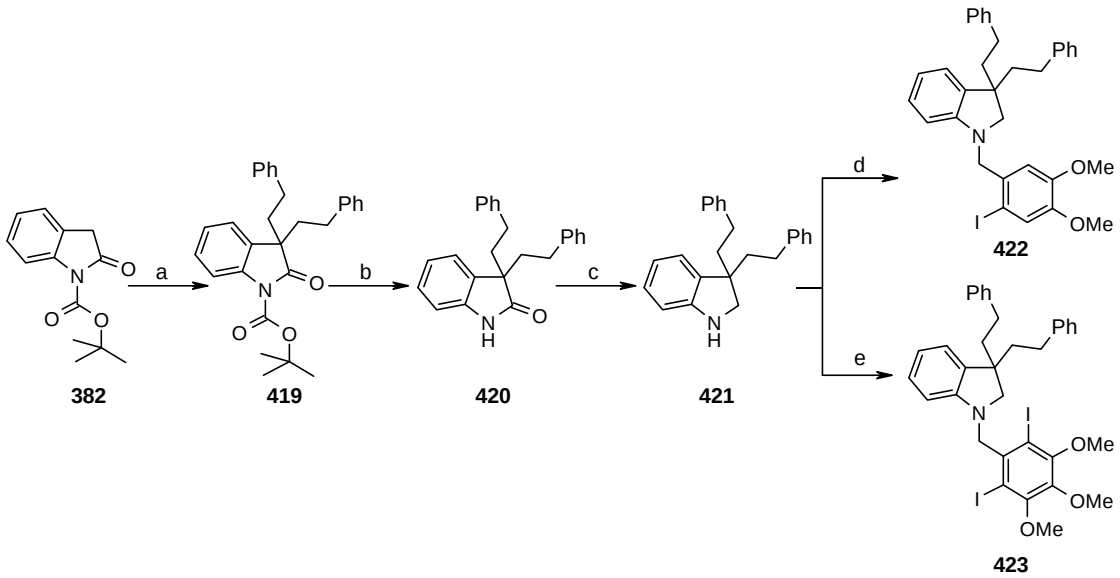


416 **418** **411**

Scheme 103

Further studies on the C2-indoline radical

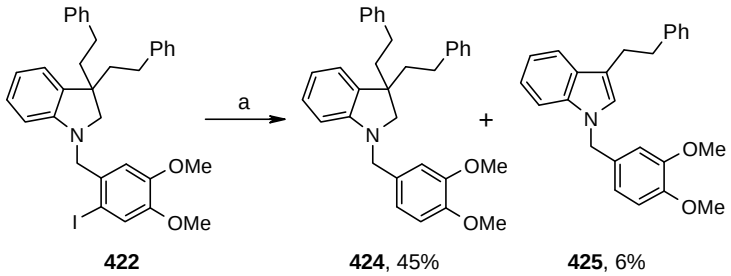
To further examine the chemistry of the C2-indoline radical, we decided to prepare the related homobenzyl derivatives **422** and **423**. Boc-oxindole **382** was *bis*-alkylated with 2-phenylethyl bromide to give **419** in 42% yield. *N*-Deprotection to **420** and reduction to **421** furnished the indoline core structure which was subsequently coupled to benzyl chlorides **392** and **395** to give our precursors **422** and **423** respectively (Scheme 104). By introducing an additional carbon into the C3 side chains we hoped to prevent fragmentation and indole formation, and facilitate 6-*exo*/*endo*-trig cyclisation to the proximal arenes.



Scheme 104: Synthesis of model system 3.

Reagents and conditions: (a) NaH (2.5 equiv.), DMF, 2-phenylethyl bromide (2.5 equiv.), RT, 16 h, 42%; (b) TFA, CH_2Cl_2, RT, 6 h, 99%; (c) $LiAlH_4$ (1.0 M in THF), THF, 60 °C, 16 h, 68%; (d) K_2CO_3, KI, **392**, acetone, Δ, 16 h, 57%; (e) K_2CO_3, KI, **395**, acetone, Δ, 16 h, 41%.

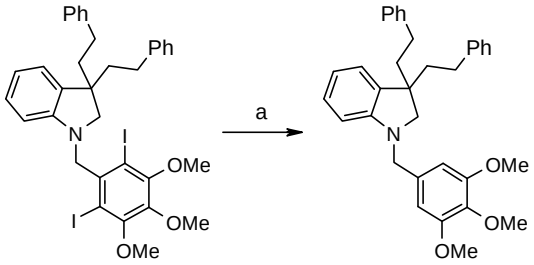
Unfortunately, treatment of mono-iodide **422** under radical forming conditions (*n*-Bu_3SnH, VAZO) produced indoline **424** as the major product together with traces of indole **425** (Scheme 105). The result showed that the rate of *H*-atom abstraction from *n*-Bu_3SnH outpaced addition of the C2-indoline radical to the pendant arene, as indeed did loss of a homobenzyl radical from C3.



Scheme 105

Reagents and conditions: (a) *n*-Bu_3SnH (2.2 equiv.), VAZO (20 mol%), PhMe, 120 °C, 3 h.

Treatment of di-iodide **423** under radical forming conditions provided a complex product mixture from which the reduction product **426** was isolated in 26% yield (Scheme 106).



423 **426**

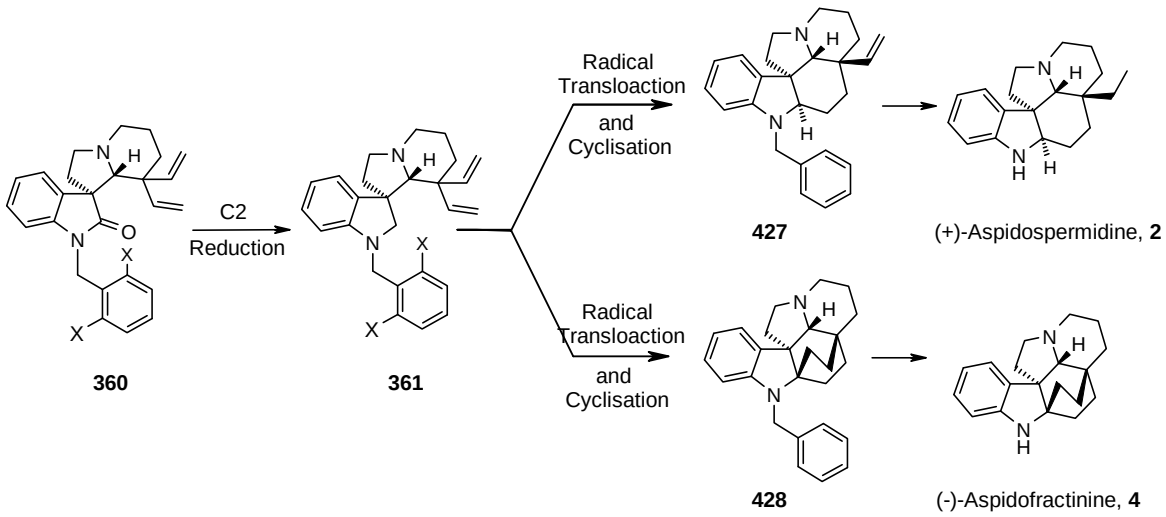
Scheme 106

Reagents and conditions: (a) *n*-Bu_3SnH (4.4 equiv.), VAZO (20 mol%), PhMe, 120 °C, 6 h, 26%.

Conclusions

This study was undertaken to discover whether intramolecular translocation of an aryl radical to C2 of an indoline, by 1,5-*H* atom abstraction, was a feasible means of elaborating this centre. Having achieved this CH activation, we also wished to show that the C2-indoline radical could promote cyclisation to a pendant alkene and to determine whether this was a facile process. Pleasingly, the radical reactions of the initial model systems **396** and **397** showed that translocation and subsequent cyclisation were indeed promoted. More importantly, they showed that a doubly primed benzyl substituent, as in **398**, promotes CH_2 double activation of the C2 centre, furnishing a propellane **401**.

Work on the project continues, with the immediate aim of effecting the reduction of oxindole **360** to **361**, keeping the aryl halide and E ring intact. With a synthesis of the indoline core realized, prospects are good for the radical induced CH activation and cyclisation approach to aspidospermidine **2** (hydrogenation and hydrogenolysis of **427** completing the total synthesis). Incorporation of a benzyl group with two *ortho* halides should also facilitate CH_2 double activation of the indoline and a tandem radical cyclisation to install rings C and F of aspidofractinine **4** (Scheme 107).



Scheme 107: Proposed future work towards the targets.

Chapter 5 - Experimental

General experimental

All reactions were performed in oven-dried glassware and when required under an inert atmosphere of nitrogen or argon. Thermolysis reactions using microwave irradiation were carried out in a CEM Discover microwave reactor operating at a power of 150W.

All solvents were distilled prior to use. Toluene, diethyl ether and THF were distilled from sodium with benzophenone as an indicator. Chloroform and dichloromethane were distilled from calcium hydride immediately prior to use. Other solvents and reagents were purified according to standard laboratory methods.

Thin Layer Chromatography (Analytical TLC) was performed using aluminium-backed plates coated with silica gel 60 containing a fluorescence indicator active at 254 nm. The plates were visualised under a UV lamp (254 nm) and by staining with either 20% phosphomolybdic acid in ethanol or 10% aqueous potassium permanganate. Column chromatography was achieved using Apollo silica gel (0.040-0.063 mm, 230-400 mesh), which was slurry packed and run under low pressure.

Infrared spectroscopy was performed using a Bio-Rad FT-IR goldengate spectrometer. Absorption maxima (ν_{max}) are quoted as wavenumbers (cm^{-1}) and the following abbreviations used to describe their intensity: w - weak, m – medium, s – strong, b - broad, v- very.

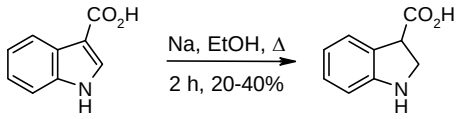
Nuclear magnetic resonance spectroscopy was performed using a Bruker Avance 300 MHz spectrometer or a Bruker DPX 400 MHz spectrometer, run in dry $CDCl_3$, CD_3OD or d^6-DMSO. Chemical shifts are quoted as δ-values in ppm downfield of TMS (0 ppm) and referenced to the solvent peak – 7.27 ppm for ^1H spectra and 77.20 ppm for ^{13}C spectra for $CDCl_3$. Coupling constants (*J*) are given in Hz and signals are described using the notation: s – singlet, d – doublet, t – triplet, q – quartet, quin. – quintet, m – multiplet, b – broad, app. – apparent and obsc. – obscured.

Mass spectrometry was performed using electron ionisation (EI) and chemical ionisation (CI) on a Thermoquest Trace GCMS spectrometer; and by electrospray positive (ES^+) ionisation on a Waters ZMD spectrometer. High resolution EIMS was performed on a VG Analytical 70-250-Se spectrometer and high resolution ESMS performed on a Bruker Apex III spectrometer.

Melting points were determined using a Griffin melting point apparatus and are uncorrected.

Synthetic Procedures–Chapter 2

2,3-Dihydro-1*H*-indole-3-carboxylic acid (246a).



247a
$C_9H_7NO_2$
(161.16)

246a
$C_9H_9NO_2$
(163.18)

Sodium metal (8.06 mmol, 1.85 g) was added to a rapidly refluxing solution of indole-3-carboxylic acid **247a** (6.20 mmol, 1.00 g) in anhydrous ethanol (40 mL). The mixture was heated at reflux under nitrogen for 16 h, allowed to cool and quenched by the careful drop-wise addition of water (40 mL). The volatiles were removed *in vacuo* before acidifying the aqueous residue to pH 1 (2 M HCl) and extracting with ethyl acetate (3 x 30 mL). The aqueous phase was then adjusted to pH 4 (2 M NaOH) and extracted with ethyl acetate (5 x 30 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* to provide the indoline product **246a** (2.34 mmol, 0.38 g, 38%) as a light brown solid. Data consistent with the literature.[46]

IR (ATR / golden gate): 3296 (m), 3126 (w), 3013 (w), 3062 (w), 2847 (w), 1622 (s), 1519 (m), 1442 (m).

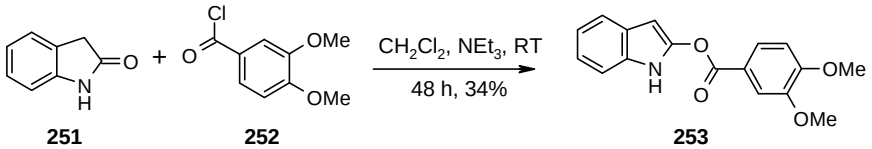
^{1}H NMR (300 MHz, DMSO-d_6)

δ ppm 7.16 (1H, m, aromatic C**H**), 6.97 (1H, m, aromatic C**H**), 6.56 (1H, dd, *J*=7.7, 0.9 Hz, aromatic C**H**), 6.51 (1H, d, *J*=7.7 Hz, aromatic C**H**), 4.07 (1H, app. td, *J*=8.0, 1.0 Hz, C**H**CO_2H), 3.67 (1H, dd, *J*=9.6, 7.8 Hz, NC**H**HCHCO_2H), 3.57 (1H, app t, *J*=9.6 Hz, CH**H**CHCO_2H), 1.91 (1H, s, N**H**).

^{13}C NMR + DEPT (75 MHz, DMSO-d_6)

δ ppm 173.5 (**C**=O), 152.0 (**C**), 128.1 (**C**H), 126.3 (**C**), 124.6 (**C**H), 116.8 (**C**H), 108.8 (**C**H), 48.5 (**C**H_2), 46.6 (**C**H).

(3,4-Dimethoxyphenyl)-(2-hydoxy-indol-1-yl)-methanone (253).



251 C_8H_7NO (133.15)

252 $C_9H_9ClO_3$ (200.62)

253 $C_{17}H_{15}NO_4$ (297.31)

To a solution of oxindole (**251**) (1.5 mmol, 0.20 g) and triethylamine (1.5 mmol, 0.21 mL) in anhydrous dichloromethane (20 mL) under nitrogen at room temperature was added a solution of 3,4-dimethoxybenzoyl chloride (**252**) (1.5 mmol, 0.30 g) in anhydrous dichloromethane (20 mL). The reaction mixture was stirred for 48 h at room temperature, then washed with water (50 mL). The organic phase was dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 25% diethyl ether in petroleum ether) to give the indole (**253**) (0.5 mmol, 0.15 g, 34%) as a white solid.

Novel

Mpt: 172–173 °C (Et_2O).

IR (ATR / golden gate): 3343 (s), 3134 (w), 3077 (w), 2978 (w), 2933 (w), 1736 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

δ ppm 8.84 (1H, b s, NH), 7.86 (1H, dd, *J*=8.3, 2.0 Hz, aromatic C**H**), 7.65 (1H, d, *J*=2.0 Hz, aromatic C**H**), 7.57 (1H, d, *J*=8.3 Hz, aromatic C**H**), 7.32 (1H, d, *J*=7.7 Hz, aromatic C**H**), 7.21–7.11 (2H, m, 2 x aromatic C**H**), 6.95 (1H, d, *J*=8.6 Hz, aromatic C**H**), 6.28 (1H, d, *J*=1.5 Hz, aromatic C**H**), 3.97 (6H, s, 2 x OC**H**$_3$).

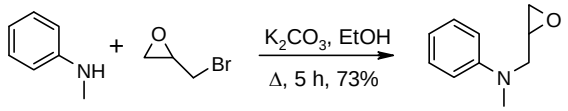
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 163.8 (**C**=O), 154.5 (**C**), 149.3 (**C**), 143.9 (**C**), 131.7 (**C**), 127.0 (**C**), 125.1 (**C**H), 121.1 (**C**H), 121.0 (**C**), 120.7 (**C**H), 120.6 (**C**H), 112.8 (**C**H), 111.1 (**C**H), 110.9 (**C**H), 88.1 (**C**H), 56.5 (2xO**C**H$_3$).

ESMS: *m/z* (%): 320 $[M+Na]^+$ (100), 298 $[M+H]^+$ (40).

HRMS (ES +ve): $C_{17}H_{15}NNaO_4$ $[M+Na]^+$ 320.0893, found 320.0891.

Methyl-oxiranylmethyl-phenylamine (255).



254 C_7H_9N (107.16) **429** C_3H_5BrO (136.98) **255** $C_{10}H_{13}NO$ (163.22)

N-Methylaniline (0.93 mmol, 0.1 mL) (**254**) was dissolved in ethanol (10 mL) with potassium carbonate (1.86 mmol, 0.26 g) and stirred under nitrogen at room temperature for 1 h. Epibromohydrin **429** (2.79 mmol, 0.24 mL) was added to the reaction mixture drop-wise and then stirred at reflux for 5 h. Ethanol was removed *in vacuo* and the crude material partitioned between water (10 mL) and ethyl acetate (10 mL). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 10% ethyl acetate in hexanes) to give the epoxide **255** as a yellow oil (0.67 mmol, 0.11 g, 73%). Data consistent with the literature.[64]

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

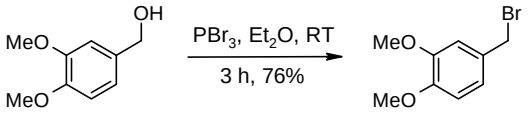
δ ppm 7.29–7.22 (2H, m, 2 x aromatic C**H**), 6.79–6.73 (3H, m, 3 x aromatic C**H**), 3.65 (1H, dd, *J*=15.7, 3.2 Hz, OC**H**$_2$CHCH$_2$N), 3.41 (1H, dd, *J*=15.7, 4.8 Hz, OC**H**$_2$CHCH$_2$N), 3.17 (1H, m, OCH$_2$C**H**CH$_2$N), 3.01 (3H, s, NC**H**$_3$), 2.79 (1H, app. t, *J*=4.8 Hz,OCH$_2$CHC**H**HN), 2.57 (1H, dd, *J*=4.8, 2.7 Hz, OCH$_2$CHCH**H**N).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 149.9 (**C**), 129.6 (2x**C**H), 117.3 (**C**H), 112.8 (2x**C**H), 54.6 (**C**H$_2$), 50.9 (**C**H), 45.5 (**C**H$_2$), 39.4 (N**C**H$_3$).

EIMS: *m/z* (%): 163 $[M]^{+\cdot}$ (80), 120 $[M\text{-}C_2H_3O]^{+\cdot}$ (100), 104 (80), 77 (65).

2-Bromomethyl-1,2-dimethoxy-benzene (261).



390
$C_9H_{12}O_3$
(168.19)

261
$C_9H_{11}BrO_2$
(231.09)

To a solution of 3,4-dimethoxybenzyl alcohol (**390**) (2.5 mmol, 0.36 mL) in anhydrous ether (30 mL) at 0 °C was added a solution of phosphorus tribromide (5.0 mmol, 0.49 mL) in dry ether (5 mL) drop-wise. The reaction mixture was stirred at room temperature for 3 h before pouring slowly into water (20 mL) and extracting with dichloromethane (3 x 20 mL). The dried ($MgSO_4$) organic phase was concentrated *in vacuo* to give a white solid that was washed with hexane to give benzyl bromide (**261**) (1.9 mmol, 0.44 g, 76%) as a white solid with no further need for purification. Data consistent with the literature.[65]

IR (ATR / golden gate): 3007 (w), 2932 (w), 2834 (w), 1602 (m), 1511 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

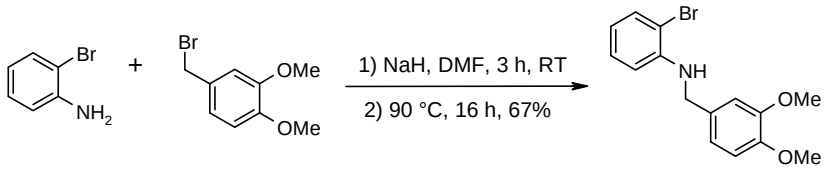
δ ppm 6.94 (1H, dd, *J*=8.1, 2.1 Hz, aromatic C**H**), 6.92 (1H, app. s, aromatic C**H**), 6.51 (1H, d, *J*=8.1 Hz, aromatic C**H**), 4.50 (2H, s, BrC**H**$_2$Ar), 3.89 (3H, s, OC**H**$_3$), 3.88 (3H, s, OC**H**$_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 149.0 (**C**), 148.9 (**C**), 130.0 (**C**), 121.3 (**C**H), 111.9 (**C**H), 110.8 (**C**H), 55.7 (O**C**H$_3$), 55.6 (O**C**H$_3$), 34.1 (**C**H$_2$).

EIMS: *m/z* (%): 230:232 {1:1} $[M]^{+\cdot}$ Br^{79}:Br^{81} (20), 151 $[M\text{-}Br]^{+\cdot}$ (100), 137 (20), 107 (50), 77 (45).

(2-Bromophenyl)-(3,4,dimethoxy-benzyl)-amine (258).



257
C_6H_6BrN
(172.03)

261
$C_9H_{11}BrO_2$
(231.09)

258
$C_{15}H_{16}BrNO_2$
(322.20)

To a solution of 2-bromoaniline (**257**) (2.90 mmol, 0.50 g) in anhydrous DMF (40 mL) at room temperature under nitrogen was added sodium hydride (60% dispersion in mineral oil, 5.33 mmol, 0.13 g) and the reaction mixture stirred for 3 h. To the reaction mixture (purple/brown solution) was added a solution of benzyl bromide **261** (3.77 mmol, 0.87 g) in anhydrous DMF (10 mL) drop-wise. The reaction mixture was heated at 90 °C for 16 h, then cooled to 0 °C and partitioned between water (20 mL) and ethyl acetate (20 mL). The organic phases were washed with water (4 x 20 mL) and brine (20 mL), dried ($MgSO_4$) and purified by column chromatography (silica, 10% diethyl ether in petroleum ether) to give **258** as a pale yellow solid (1.96 mmol, 0.63 g, 67%).

Novel

Mpt: 86–87 °C (EtOH).

IR (ATR / golden gate): 3387 (m), 3003 (w), 2958 (w), 2929 (w), 2827 (w), 1509 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

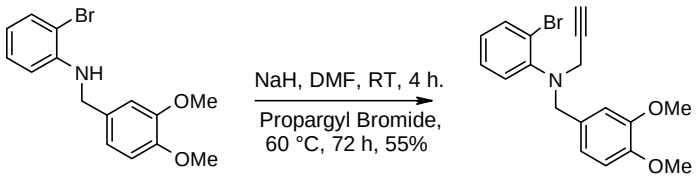
δ ppm 7.44 (1H, dd, *J*=7.9, 1.4 Hz, aromatic C**H**), 7.14 (1H, app. td, *J*=8.4, 1.4 Hz, aromatic C**H**), 6.93–6.83 (3H, m, 3 x aromatic C**H**), 6.65–6.55 (2H, m, 2 x aromatic C**H**), 4.68 (1H, b s, N**H**), 4.33 (2H, b d, *J*=5.1 Hz, NC**H**$_2$), 3.88 (3H, s, OC**H**$_3$), 3.87 (3H, s, OC**H**$_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 149.6 (**C**), 148.7 (**C**), 145.1 (**C**), 132.7 (C**H**), 131.5 (**C**), 128.8 (C**H**), 119.8 (C**H**), 118.4 (C**H**), 112.2 (C**H**), 111.7 (C**H**), 110.9 (**C**H), 110.1 (**C**-Br), 56.3 (OC**H**$_3$), 56.2 (OC**H**$_3$), 48.3 (NHC**H**$_2$).

EIMS: *m/z* (%):	321:323 {1:1} $[M]^{+\cdot}$ Br^{79}:Br^{81} (20), 151 $[M-C_6H_4BrNH]^{+\cdot}$ (100), 135 (10), 121 (16), 107 (26), 91 (19), 77 (23).
HRMS (ES +ve):	$C_{15}H_{16}BrNNaO_2$ $[M+Na]^+$ 344.0256, found 344.0250.
CHN:	Calcd for $C_{15}H_{16}BrNO_2$: C, 55.92, H, 5.01, N, 4.35. Found: C, 55.69, H, 5.04, N, 4.18.

(2-Bromophenyl)-(3,4-dimethoxy-benzyl)-prop-2-ynyl-amine (259).



258
$C_{15}H_{16}BrNO_2$
(322.20)

259
$C_{18}H_{18}BrNO_2$
(360.25)

Aniline **258** (2.9 mmol, 0.94 g) was added to a suspension of sodium hydride (60% in mineral oil, 3.2 mmol, 0.13 g) in anhydrous DMF (30 mL) at 0 °C and the dark brown solution stirred at room temperature for 4 h. Propargyl bromide solution (80% in toluene, 5.8 mmol, 0.65 mL) was added drop-wise to the reaction mixture which was then heated to 60 °C for 72 h. Water (50 mL) was carefully added to the reaction mixture and the aqueous extracted with ethyl acetate (2 x 50 mL). The organic phases were combined, washed with water (5 x 30 mL) and brine (60 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a dark brown oil. The crude was purified by column chromatography (silica, 10% diethyl ether in petroleum ether) to give an inseparable 1:1.5 mixture of the alkyne (**259**) and starting material (**258**) as a pale yellow solid (1.6 mmol, 0.58 g, 55%).

Novel

IR (ATR / golden gate): 3395 (w), 3285 (w), 3068 (w), 3003 (w), 2958 (w), (w), 2827 (w), 2353 (m), 1512 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*): (Mixture of **258**:**259**, 1.5:1)

Data for **259**:

δ ppm 7.60 (1H, dd, *J*=8.0, 1.4 Hz, aromatic C**H**), 7.34–7.24 (2H, m, 2 x aromatic C**H**), 7.17–7.11 (2H, m, aromatic C**H**), 7.00–6.79 (2H, m, 2 x aromatic C**H**), 4.27 (2H, s, C**H**$_2$Ar), 3.88–3.86 (6H, m, 2 x OC**H**$_3$), 3.80 (2H, app. d, *J*=2.4 Hz, NC**H**$_2$C≡CH), 2.25 (1H, app. t, *J*=2.3 Hz, NCH$_2$C≡C**H**).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*): (Mixture of **258**:**259**, 1.5:1)

Data for **259**:

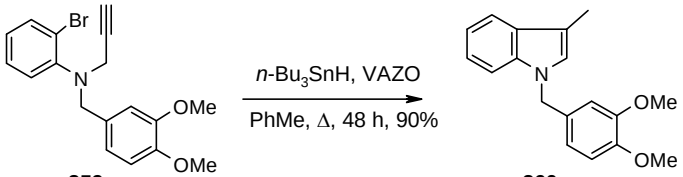
δ ppm 149.2 (**C**), 148.5 (**C**), 133.7 (**C**H), 131.4 (**C**), 130.5 (**C**), 128.0 (**C**H), 125.7 (**C**H), 125.0 (**C**H), 121.5

(**C**), 120.9 (**C**H), 111.9 (**C**H), 110.8 (**C**H), 79.1 (**C**), 73.5 (**C**H), 56.1 (O**C**H_3), 56.0 (O**C**H_3), 55.5 (**C**H_2), 41.9 (**C**H_2).

ESMS: *m/z* (%): 382:384 {1:1} $[M + Na]^+$ Br^{79}:Br^{81} (80).

HRMS (ES +ve): $C_{18}H_{18}BrNNaO_2$ $[M+Na]^+$ 382.0413, found 382.0421.

1-(3,4-dimethoxy-benzyl)-3-mehtyl-1*H*-indole (260).



259
$C_{18}H_{18}BrNO_2$
(360.25)

260
$C_{18}H_{19}NO_2$
(281.36)

The crude mixture of alkyne **259** and **258** (1:1.5) (0.20 g) was dissolved in anhydrous toluene (30 mL) along with tributyltin hydride (1.17 mmol, 0.31 mL) and VAZO (3 mg) and stirred under nitrogen at reflux for 16 h. The reaction mixture was cooled and further tributyltin hydride (1.17 mmol, 0.31 mL) and VAZO (3 mg) added. The reaction mixture was again heated to reflux and stirred under nitrogen for a further 24 h. Once cooled, the solvent was removed *in vacuo* and the crude residue re-dissolved in ether (30 mL) and stirred vigorously with a saturated aqueous solution of KF (50 mL) for 30 min. The organic phase was separated and washed with water (50 mL) and brine (50 mL) and dried ($MgSO_4$). The crude residue was purified by column chromatography (10% anhydrous K_2CO_3: 90% silica, 10% diethyl ether in petroleum ether) to give indole (**260**)[63] (0.28 mmol, 0.08 g, 90% based on available starting material) as a brown solid.

Mpt: 58–60 °C (EtOAc).

IR (ATR / golden gate): 3395 (m), 3354 (w), 3068 (w), 2995 (w), 2958 (w), 2929 (w).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

δ ppm 7.27 (1H, m, aromatic C**H**), 7.19 (1H, m, aromatic C**H**), 7.10 (1H, dd, *J*=7.4, 1.7 Hz, aromatic C**H**), 6.96-6.92 (2H, m, 2 x aromatic C**H**), 6.78 (1H, app. td, *J*=7.4, 1.0 Hz, aromatic C**H**), 6.73-6.65 (2H, m, 2 x aromatic C**H**), 3.93 (3H, s, OC**H**$_3$), 3.89 (3H, s, OC**H**$_3$), 3.89-3.88 (2H, obsc. m, C**H**$_2$Ar), 2.81 (3H, s, C**H**$_3$).

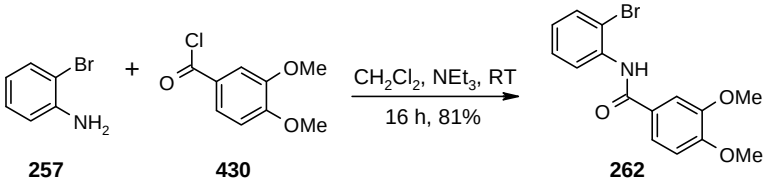
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 149.6 (**C**), 148.6 (**C**), 146.8 (**C**), 132.4 (**C**), 130.3 (**C**H), 129.6 (**C**H), 128.9 (**C**H), 127.8 (**C**),

121.9 (**C**H), 117.1 (**C**H), 113.3 (**C**H), 111.9 (**C**H), 110.1 (**C**H), 56.3 (O**C**H_3), 56.2 (O**C**H_3), 48.6 (N**C**H_2), 31.2 (**C**H_3).

N.B. 1 x aromatic (**C**) not observed.

***N*-(2-Bromophenyl)-3,4-dimethoxybenzamide (262).**



257 C_6H_6BrN (172.03)

430 $C_9H_9ClO_3$ (200.62)

262 $C_{15}H_{14}BrNO_3$ (336.19)

To a solution of 2-bromoaniline (**257**) (1.16 mmol, 0.20 g) and triethylamine (1.16 mmol, 0.16 mL) in anhydrous dichloromethane (20 mL) under nitrogen at room temperature was added a solution of 3,4-dimethoxybenzoyl chloride (**430**) (1.16 mmol, 0.23 g) in anhydrous dichloromethane (20 mL). The reaction mixture was stirred for 16 h at room temperature, then washed with water (50 mL). The organic phase was separated, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 25% diethyl ether in petroleum ether) to give the aniline (**262**) (0.94 mmol, 0.32 g, 81%) as a white solid. Data consistent with the literature.[66]

IR (ATR / golden gate): 3560 (w), 3269 (w), 3019 (w), 2946 (w), 1647 (s), 1509 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 8.54 (1H, dd, *J*=8.3, 1.4 Hz, aromatic C**H**), 8.43 (1H, b s, N**H**), 7.58 (1H, dd, *J*=8.2, 1.5 Hz, aromatic C**H**), 7.55 (1H, d, *J*=2.1 Hz, aromatic C**H**), 7.49 (1H, dd, *J*=8.3, 2.1 Hz, aromatic C**H**), 7.42 (1H, app. td, *J*=7.8, 1.4 Hz, aromatic C**H**), 7.01 (1H, app. td, *J*=7.8, 1.5 Hz, aromatic C**H**), 6.96 (1H, d, *J*=8.2 Hz, aromatic C**H**), 3.98 (3H, s, OC**H**$_3$), 3.96 (3H, s, OC**H**$_3$).

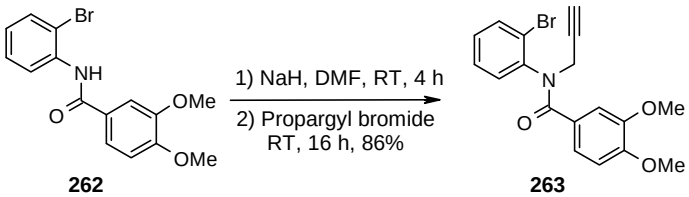
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 165.0 (**C**=O), 152.6 (**C**), 149.5 (**C**), 136.2 (**C**), 132.4 (**C**H), 128.7 (**C**H), 127.4 (**C**), 125.2 (**C**H), 121.8 (**C**H), 119.8 (**C**H), 113.8 (**C**), 111.0 (**C**H), 110.8 (**C**H), 56.3 (2xO**C**H$_3$).

ESMS: *m/z* (%): 358:360 {1:1} $[M + Na]^+$ Br^{79}:Br^{81} (100).

HRMS (ES +ve): $C_{15}H_{15}BrNO_3$ $[M+H]^+$ 336.0230, found 336.0233.

***N*-(2-Bromophenyl)-3,4-dimethoxy-*N*-prop-2-ynyl-benzamide (263).**



262
$C_{15}H_{14}BrNO_3$
(336.19)

263
$C_{18}H_{16}BrNO_3$
(374.24)

To a suspension of sodium hydride (60% in mineral oil, 0.94 mmol, 0.04 g) in anhydrous DMF (10 mL) under nitrogen was added aniline **262** (0.63 mmol, 0.21 g). The reaction mixture was stirred for 4 h at room temperature then propargyl bromide (80% solution in toluene, 0.94 mmol, 0.08 mL) was added drop-wise. After 16 h water (20 mL) was added and the aqueous phase extracted with ethyl acetate (2 x 20 mL). The combined organic phases were washed with water (5 x 20 mL), brine (30 mL), ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 50% diethyl ether in petroleum ether) to give the alkyne (**263**) as a white solid (0.54 mmol, 0.20 g, 86%).

Novel

Mpt: 145-146 °C (EtOH).

IR (ATR / golden gate): 3253 (m), 3085 (w), 3056 (w), 2999 (w), 2954 (w), 2929 (w), 2353 (m), 1644 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

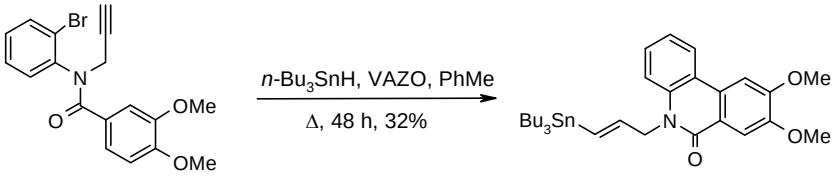
δ ppm 7.60 (1H, d, *J*=8.2 Hz, aromatic C**H**), 7.23-6.95 (5H, m, 5 x aromatic C**H**), 6.65 (1H, d, *J*=8.2 Hz, aromatic C**H**), 5.09 (1H, b d, *J*=17.4 Hz, HC≡CC**H**H), 4.12 (1H, dd, *J*= 17.4, 2.4 Hz, HC≡CCH**H**), 3.80 (3H, s, OC**H**$_3$), 3.70 (3H, s, OC**H**$_3$), 2.21 (1H, t, *J*=2.4 Hz, **H**C≡CCH_2).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 170.3 (**C**=O), 151.0 (**C**), 148.3 (**C**), 141.9 (**C**), 133.9 (**C**H), 132.5 (**C**H), 129.7 (**C**H), 128.7 (**C**H), 127.3 (**C**), 123.2 (**C**H), 122.6 (**C**), 112.1 (**C**H), 110.3 (**C**H), 78.2 (**C**), 72.8 (C≡**C**H), 56.1 (2xO**C**H_3), 38.7 (N**C**H_2C≡CH).

EIMS: *m/z* (%):	373:375 {1:1} $[M]^{+\cdot}$ Br^{79}:Br^{81} (20), 294 $[M\text{-}Br]^{+\cdot}$ (50), 165 $[COC_6H_3(OCH_3)_2]^{+\cdot}$ (100), 137 (45), 122 (29), 107 (24), 92 (27), 77 (65).
HRMS (ES +ve):	$C_{18}H_{16}BrNNaO_3$ $[M+Na]^+$ 396.0206, found 396.0197.
CHN:	Calcd for $C_{18}H_{16}BrNO_3$: C, 57.77, H, 4.31, N, 3.74. Found: C, 57.84, H, 4.38, N, 3.61.

8,9-Dimethoxy-5-((*E*)-3-tributylstannyl-allyl)-5*H*-phenanthridin-6-one (264).



263
$C_{18}H_{16}BrNO_3$
(374.24)

264
$C_{30}H_{43}NO_3Sn$
(584.37)

Alkyne **263** (0.27 mmol, 0.10 g), tributyltin hydride (0.56 mmol, 0.16 mL) and VAZO (3 mg) in toluene (30 mL) was heated at reflux under nitrogen for 16 h then cooled to room temperature. Further tributyltin hydride (0.56 mmol, 0.16 mL) and VAZO (3 mg) were added. After 48 h at reflux the reaction mixture was cooled to room temperature, concentrated, re-dissolved in ether (30 mL) and stirred vigorously with a saturated aqueous solution of KF (50 mL) for 30 min. The organic phase was separated, washed with water (50 mL) and brine (50 mL) and dried ($MgSO_4$). The crude residue was purified by column chromatography (10% anhydrous K_2CO_3: 90% silica, 25% diethyl ether in petroleum ether) to give tricycle **264** as a white oil (0.09 mmol, 55 mg, 32%).

Novel

IR (ATR / golden gate): 2954 (s), 2922 (s), 2872 (m), 2852 (m), 1645 (s), 1609 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

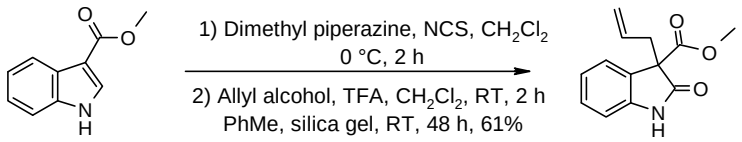
δ ppm 8.03 (1H, d, *J*=8.0 Hz, aromatic C**H**), 7.85 (1H, s, aromatic C**H**), 7.50 (1H, s, aromatic C**H**), 7.33–7.24 (2H, m, 2 x aromatic C**H**), 7.16 (1H, m, aromatic C**H**), 5.97–5.96 (2H, m, C**H**=C**H**), 4.99 (2H, b s, NC**H**$_2$), 3.97 (3H, s, OC**H**$_3$), 3.92 (3H, s, OC**H**$_3$), 1.34–1.26 (6H, m, Sn(C**H**$_2$CH$_2$CH$_2$CH$_3$)$_3$), 1.16–1.09 (6H, m, Sn(CH$_2$C**H**$_2$CH$_2$CH$_3$)$_3$), 0.76–0.69 (15H, m, Sn(CH$_2$CH$_2$C**H**$_2$C**H**$_3$)$_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 161.2 (**C**=O), 153.7 (**C**), 150.2 (**C**), 141.8 (**C**H), 137.3 (**C**), 131.2 (**C**H), 128.9 (**C**), 128.7 (**C**H), 122.9

	(**C**H), 122.5 (**C**H), 120.0 (**C**), 119.6 (**C**), 116.7 (**C**H), 109.6 (**C**H), 103.0 (**C**H), 56.5 (O**C**H_3), 56.5 (O**C**H_3), 48.4 (N**C**H_2), 29.4 (3x**C**H_2), 27.5 (3x**C**H_2), 14.0 (3x**C**H_3), 9.8 (3x**C**H_2).
ESMS: *m/z* (%):	1192 $[M_2+Na]^+$ (20), 608 $[M+Na]^+$ (20).
HRMS (ES +ve):	$C_{30}H_{43}NNaO_3Sn$ $[M+Na]^+$ 608.2157, found 608.2161.

Methyl 3-allyl-2-oxo-2,3-dihydro-1*H*-indol-3-carboxylate (266).



265
$C_{10}H_9NO_2$
(175.19)

266
$C_{13}H_{13}NO_3$
(231.25)

To a solution of methyl indole-3-carboxylate (**265**) (57.1 mmol, 10.0 g) in anhydrous DCM (300 mL) at 0 °C under nitrogen was added sequentially dimethyl piperazine (32.0 mmol, 4.3 mL) and NCS (62.7 mmol, 8.4 g). After 2 h the reaction mixture was added to a solution of allyl alcohol (114.2 mmol, 7.8 mL) and TFA (13.7 mmol, 1.0 mL) in dry DCM (150 mL),at a rate sufficient to maintain the reaction temperature below 25 °C. After 2 h at room temperature the reaction mixture was washed with $NaHCO_3$ (10%, 2 x 100 mL) and HCl (0.5 M, 2 x 100 mL). The organic phases were dried ($MgSO_4$), concentrated *in vacuo*, then re-dissolved in anhydrous toluene (300 mL) and stirred with silica gel at room temperature under nitrogen for 4 days. The reaction mixture was filtered, concentrated *in vacuo* to a brown oil then recrystallised from 40% ethyl acetate in hexane to give the desired product (**266**) as white crystals (19.5 mmol, 4.50 g, 61%). Data consistent with the literature.[54]

Mpt: 129–131 °C (EtOAc and hexanes) (Lit.[54] 130–132 °C)

IR (ATR / golden gate): 3158 (b m), 3093 (b m), 3036 (w), 2942 (w), 2876 (w), 2819 (w), 1739 (s), 1719 (s), 1681 (s), 1619 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

δ ppm 9.03 (1H, b s, N**H**), 7.31–7.27 (2H, m, 2 x C**H** aromatic), 7.08 (1H, app. t, *J*=7.5 Hz, C**H** aromatic), 6.97 (1H, d, *J*=8.3 Hz, C**H** aromatic), 5.48 (1H, ddt, *J*=17.1, 10.1, 7.5 Hz, CH_2=C**H**), 5.09 (1H, d, *J*=17.1 Hz, C**H**H=CH), 4.99 (1H, dd, *J*=10.1, 0.6 Hz, CH**H**=CHCH_2C), 3.72 (3H, s, COOC**H**$_3$), 3.09-2.96 (2H, m, =CHC**H**$_2$C).

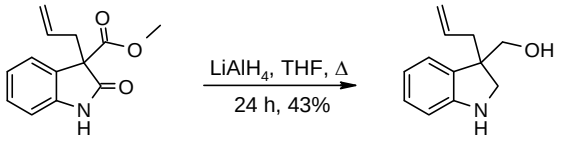
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 176.5 (**C**=O), 169.7 (**C**=O), 141.7 (**C**), 131.1 (**C**H), 129.5 (**C**H), 128.4 (**C**), 124.3 (**C**H), 123.1 (**C**H),

120.3 (**C**CH_2), 110.6 (**C**H), 60.0 (**C**), 53.4 (O**C**H_3), 38.8 (**C**H_2).

ESMS: *m/z* (%): 254 $[M+Na]^+$ (100).

(3-Allyl-2,3-dihydro-1*H*-indol-3-yl)-methanol (271).



266
$C_{13}H_{13}NO_3$
(231.25)

271
$C_{12}H_{15}NO$
(189.26)

To anhydrous THF (150 mL) at 0 °C under nitrogen was added sequentially $LiAlH_4$ (73.5 mmol, 2.79 g) and a solution of amide **266** (14.7 mmol, 3.4 g) in dry THF (100 mL) drop-wise over 10 min. The reaction mixture was refluxed under nitrogen for 16 h then cooled to 0 °C and water (50 mL) added cautiously. The reaction mixture was concentrated to half its volume then filtered and partitioned between ether (50 mL) and water (50 mL). The aqueous phase was extracted with ether (3 x 70 mL), then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 25% diethyl ether in petroleum ether) to give the alcohol (**271**) (6.34 mmol, 1.20 g, 43%) as a pale brown oil.

Novel

IR (ATR / golden gate): 3334 (b m), 2905 (m), 2868 (m), 2353 (m), 2333 (m), 1605 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

δ ppm 7.11–7.05 (2H, m, 2 x aromatic C**H**), 6.76 (1H, app. td, *J*=7.5, 0.8 Hz, aromatic C**H**), 6.65 (1H, dd, *J*=7.5, 0.9 Hz, aromatic C**H**), 5.75 (1H, ddt, *J*=17.2, 10.1, 7.3 Hz, CH_2=C**H**), 5.14–5.06 (2H, m, C**H**$_2$=CH), 3.71 (1H, d, *J*=10.9 Hz, C**H**HOH or C**H**HNH), 3.65 (1H, d, *J*=10.9 Hz, C**H**HOH or C**H**HNH), 3.48 (1H, d, *J*=9.4 Hz, CH**H**OH or CH**H**NH), 3.44 (1H, d, *J*=9.4 Hz, CH**H**OH or CH**H**NH), 2.49 (2H, d, *J*=7.3 Hz, =CHC**H**$_2$C).

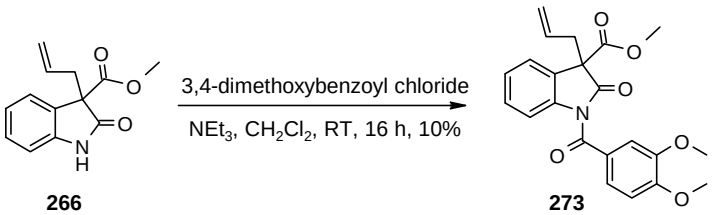
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 152.1 (**C**), 134.6 (**C**H), 132.1 (**C**), 128.6 (**C**H), 123.9 (**C**H), 118.9 (**C**H), 118.3 (**C**H_2), 110.2 (**C**H), 68.0 (**C**H_2), 54.3 (**C**H_2), 51.3 (**C**), 40.3 (**C**H_2).

ESMS: *m/z* (%): 190 $[M+H]^+$ (40), 212 $[M+Na]^+$ (100).

HRMS (ES +ve): $C_{12}H_{16}NO$ $[M+H]^+$ 190.1226, found 190.1225.

Methyl 3-allyl-1-(3,4-dimethoxy-benzoyl)-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylate (273).



266
$C_{13}H_{13}NO_3$
(231.25)

273
$C_{22}H_{21}NO_6$
(395.42)

To a solution of amide (**266**) (0.87 mmol, 0.20 g) and triethylamine (0.87 mmol, 0.12 mL) in anhydrous DCM (50 mL) at room temperature under nitrogen was added a solution of 3,4-dimethoxybenzoyl chloride (0.87 mmol, 0.18 g) in DCM (50 mL). After 16 h the reaction mixture was washed with water (50 mL) and the aqueous phase extracted with DCM (3 x 50 mL). The combined organic phasess were washed with brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 20% diethyl ether in petroleum ether) to give amide (**273**) (0.08 mmol, 33 mg, 10%) as a white solid.

Novel

Mpt: 103-105 °C (EtOAc).

IR (ATR / golden gate): 3166 (w), 3089 (w), 3007 (w), 2357 (w), 2329 (w), 1740 (s), 1723 (s), 1671 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

δ ppm 7.69 (1H, d, *J*=7.9 Hz, aromatic C**H**), 7.52 (1H, dd, *J*=8.4, 2.2 Hz, aromatic C**H**), 7.43–7.36 (3H, m, 3 x aromatic C**H**), 7.23 (1H, app. dt, *J*=7.6, 1.0 Hz, aromatic C**H**), 6.92 (1H, d, *J*=8.4 Hz, aromatic C**H**), 5.45 (1H, dddd, *J*=16.9, 9.9, 8.2, 6.4 Hz, CH_2=C**H**), 5.12 (1H, dd, *J*=16.9, 1.2 Hz, C**H**H=CH), 5.04 (1H, b d, *J*=9.9 Hz, CH**H**=CH), 3.96 (3H, s, OC**H**$_3$), 3.94 (3H, s, OC**H**$_3$), 3.75 (3H, s, COOC**H**$_3$), 3.14-2.97 (2H, m, =CHC**H**$_2$).

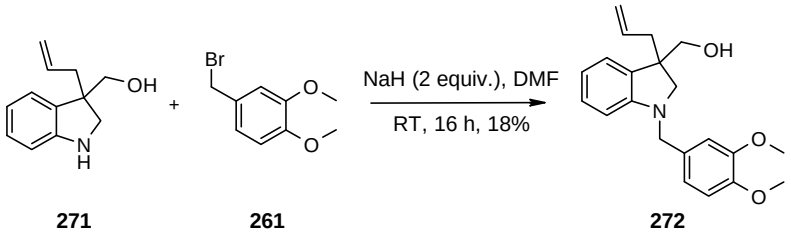
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 173.7 (**C**=O), 169.4 (**C**=O), 168.5 (**C**=O), 154.1 (**C**), 149.1 (**C**), 141.3 (**C**), 131.0 (**C**H), 129.8 (**C**H),

	127.2 (**C**), 125.9 (**C**), 125.2 (2x**C**H), 123.9 (**C**H), 120.9 (**C**H_2), 115.0 (**C**H), 113.0 (**C**H), 110.8 (**C**H), 60.4 (**C**), 56.4 (O**C**H_3), 56.4 (O**C**H_3), 53.7 (O**C**H_3), 38.7 (**C**H_2).
ESMS: *m/z* (%):	418 $[M+Na]^+$ (40).
HRMS (ES +ve):	$C_{22}H_{21}NNaO_6$ $[M+Na]^+$ 418.1261, found 418.1253.

[3-Allyl-1-(3,4-dimethoxy-benzyl)-2,3-dihydro-1*H*-indol-3-yl]-methanol (272).

Method A:

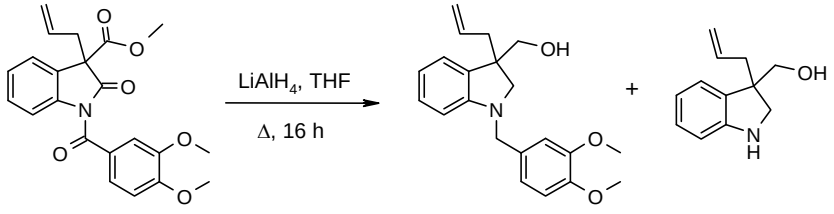


271
$C_{12}H_{15}NO$
(189.26)

261
$C_9H_{11}BrO_2$
(231.09)

272
$C_{21}H_{25}NO_3$
(339.44)

Method B:



273
$C_{22}H_{21}NO_6$
(395.42)

272, 11%
$C_{21}H_{25}NO_3$
(339.44)

271, 63%
$C_{15}H_{15}NO$
(189.26)

Method A: To a solution of amine (**271**) (1.06 mmol, 0.20 g) in dry DMF (30 mL) under nitrogen at 0 °C was added sodium hydride (60% dispersion in mineral oil, 2.11 mmol, 85 mg). The reaction mixture was allowed to warm to room temperature over 2 h (reaction mixture turns from purple to brown) then benzyl bromide (**261**) (1.06 mmol, 0.25 g) in dry DMF (20 mL) was added drop-wise. After 16 h water (50 mL) was added. The aqueous phase was extracted with ethyl acetate (4 x 50 mL) and the combined organic phases washed with water (4 x 50 mL), brine (50 mL), dried ($MgSO_4$) and purified by column chromatography (silica, 25% diethyl ether in petroleum ether) to give the alcohol (**272**) (0.19 mmol, 65 mg, 18%) as a colourless oil.

Method B: To anhydrous THF (20 mL) at 0 °C under nitrogen was added sequentially $LiAlH_4$ (0.63 mmol, 24 mg) and a solution of amide (**273**) (0.08 mmol, 33 mg) in dry THF (5 mL) drop-wise over 3 min. The reaction mixture refluxed under nitrogen for 16 h then cooled to 0 °C and water (20 mL) added cautiously. The

reaction mixture was concentrated *in vacuo* to half its original volume, filtered and partitioned between ether (20 mL) and water (20 mL). The aqueous phase was extracted with ether (3 x 30 mL), the combined organic phases washed with brine (40 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 25% diethyl ether in petroleum ether) to give firstly the alcohol (**272**) (0.01 mmol, 3 mg, 11%) and then the alcohol **271** (0.05 mmol, 10 mg, 63%) as colourless oils.

Novel

IR (ATR / golden gate): 3195 (s), 1690 (w), 1610 (w), 1435 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

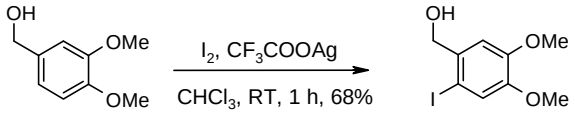
δ ppm 7.54 (1H, app. t, *J*=7.7 Hz, aromatic C**H**), 7.50 (1H, d, *J*=7.3 Hz, aromatic C**H**), 7.31–7.25 (3H, m, 3 x aromatic C**H**), 7.14 (1H, app. t, *J*=7.3 Hz, aromatic C**H**), 6.96 (1H, d, *J*=8.0 Hz, aromatic C**H**), 6.15 (1H, ddt, *J*=17.1, 10.0, 7.3 Hz, $CH_2C\mathbf{H}=CH_2$), 5.53–5.46 (2H, m, $CH=C\mathbf{H}_2$), 4.68 (1H, d, *J*=14.8 Hz, NC**H**HAr), 4.62 (1H, d, *J*=14.8 Hz, NCH**H**Ar), 4.31 (3H, s, $OC\mathbf{H}_3$), 4.28 (3H, s,$OC\mathbf{H}_3$), 4.13 (1H, d, *J*=10.8 Hz, C**H**HOH), 4.07 (1H, d, *J*=10.8 Hz, CH**H**OH), 3.69 (1H, d, *J*=9.3 Hz, NC**H**HC), 3.64 (1H, d, *J*=9.3 Hz, NCH**H**C), 2.95–2.85 (2H, m, $CH_2=CHC\mathbf{H}_2$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 152.8 (**C**), 149.5 (**C**), 148.5 (**C**), 134.6 (**C**H), 132.5 (**C**), 131.1 (**C**), 128.8 (**C**H), 123.7 (**C**H), 120.1 (**C**H), 118.2 ($\mathbf{C}H_2$), 117.9 (**C**H), 111.5 (**C**H), 111.1 (**C**H), 107.4 (**C**H), 68.0 ($\mathbf{C}H_2$), 60.5 ($\mathbf{C}H_2$), 56.2 ($O\mathbf{C}H_3$), 56.2 ($O\mathbf{C}H_3$), 52.9 ($\mathbf{C}H_2$), 49.7 (**C**), 40.3 ($\mathbf{C}H_2$).

ESMS: *m/z* (%): 362 $[M+Na]^+$ (100), 340 $[M+H]^+$ (35).

2-Iodo-4,5-dimethoxybenzyl alcohol (391).



390
$C_9H_{12}O_3$
(168.19)

391
$C_9H_{11}IO_3$
(294.09)

To a solution of 3,4-dimethoxybenzyl alcohol (**390**) (2.0 mmol, 0.3 mL) in anhydrous chloroform (10 mL) at room temperature was added silver trifluoroacetate (2.0 mmol, 0.6 g). To this suspension was added a solution of iodine (2.0 mmol, 0.5 g) in dry chloroform (60 mL) drop-wise. The reaction mixture turned a yellow/green colour and after 1 h the AgI precipitate was filtered. The resulting solution washed with $Na_2S_2O_3$ (10 mL) and concentrated *in vacuo* to afford iodide **291** as a white solid (1.3 mmol, 0.4 g, 68%). Data consistent with the literature.[67]

IR (ATR / golden gate): 3258 (m), 2903 (w), 2831 (w), 1595 (m), 1498 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

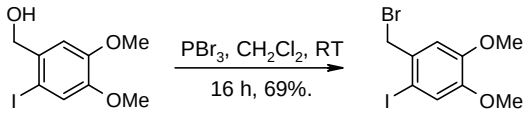
δ ppm 7.22 (1H, s, aromatic C**H**), 7.01 (1H, s, aromatic C**H**), 4.61 (2H, s, C**H**$_2$OH), 3.89 (3H, s, OC**H**$_3$), 3.86 (3H, s, OC**H**$_3$), 2.02 (1H, b s, O**H**).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 149.9 (**C**), 149.3 (**C**), 135.6 (**C**), 121.9 (**C**H), 112.1 (**C**H), 85.8 (**C**I), 69.5 (**C**H$_2$), 56.6 (O**C**H$_3$), 56.3 (O**C**H$_3$).

EIMS: *m/z* (%): 294 $[M]^{+\cdot}$ (100), 166 (15), 139 (68), 124 (28), 95 (18), 77 (20).

2-Iodo-4,5-dimethoxybenzyl bromide (271).



391
$C_9H_{11}IO_3$
(294.09)

274
$C_9H_{10}BrIO_2$
(356.99)

To a solution of alcohol (**391**) (2.95 mmol, 0.87 g) in anhydrous DCM (30 mL) under nitrogen at 0 °C was added a solution of phosphorous tribromide (5.90 mmol, 0.65 mL) in dry DCM (30 mL) drop-wise. After 16 h the reaction mixture was cooled to 0 °C water (30 mL) added, drop-wise at first. The aqueous phase was separated and extracted with DCM (3 x 30 mL). The combined organic phases were concnetrated *in vacuo* to give bromide **274** as a yellow powder (2.03 mmol, 0.73 g, 69%), which was stored in the dark at -4 °C. Data consistent with the literature.[67]

Mpt: 73–75 °C (Et_2O) (Lit.[67] 74–75°C).

IR (ATR / golden gate): 3003 (w), 2954 (w), 2929 (w), 2901 (w), 2835 (w), 1589 (m), 1500 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

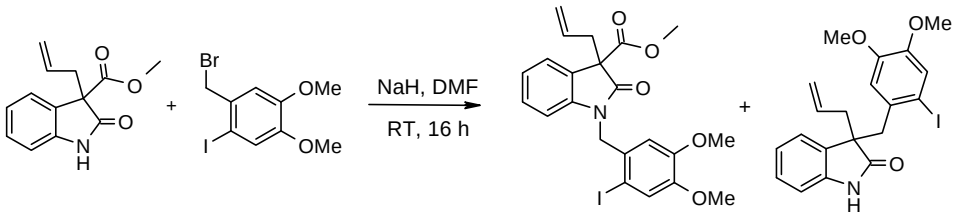
δ ppm 7.30 (1H, s, C**H** aromatic), 7.01 (1H, s, C**H** aromatic), 4.63 (2H, s, C$\mathbf{H}_2$Br), 3.92 (3H, s, OC$\mathbf{H}_3$), 3.91 (3H, s, OC$\mathbf{H}_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 150.0 (2x**C**), 132.9 (**C**), 122.3 (**C**H), 113.2 (**C**H), 88.9 (**C**I), 56.6 (O**C**H_3), 56.4 (O**C**H_3), 39.8 (**C**H_2).

EIMS: *m/z* (%): 356:358 {1:1} $[M]^{+\cdot}$ Br^{79}:Br^{81} (5), 277 $[M-Br]^{+\cdot}$ (100), 150 (11), 92 (11), 77 (11).

Methyl 3-allyl-1-(2-iodo-4,5-dimethoxy-benzyl)-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylate (275) and 3-allyl-3-(2-iodo-4,5-dimethoxy-benzyl)-1,3-dihydro-indol-2-one (276).



266
$C_{13}H_{13}NO_3$
(231.25)

274
$C_9H_{10}BrIO_2$
(356.99)

275, 24%
$C_{22}H_{22}INO_5$
(507.33)

276, 21%
$C_{20}H_{20}INO_3$
(449.29)

To a solution of amide (**266**) (2.16 mmol, 0.50 g) in dry DMF (60 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 3.24 mmol, 0.13 g) in one portion. The resulting orange / yellow solution was stirred at room temperature under nitrogen for 3 h then a solution of benzyl bromide (**274**) (2.16 mmol, 0.77 g) in dry DMF (50 mL) was added. After 16 h in the dark, water (50 mL) was added along with ether (50 mL). The separated organic phase was washed with water (5 x 50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo* and purified by column chromatography (silica, 20% diethyl ether in petroleum ether) to give firstly the desired product (**275**) (0.52 mmol, 0.26 g, 24%) as a white solid then **276** (0.45 mmol, 0.20 g, 21%) as a colourless oil.

Data for **275**.

Novel

Mpt: 127–130 °C (EtOAc).

IR (ATR / golden gate): 2995 (w), 2966 (w), 2938 (w), 2917 (w), 2831 (w), 1742 (s), 1698 (s), 1597 (m), 1502 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

δ ppm 7.30–7.27 (2H, m, 2 x aromatic C**H**), 7.22 (1H, app. td, *J*=7.8, 1.3 Hz, aromatic C**H**), 7.06 (1H, app. td, *J*=7.5, 0.9 Hz, aromatic C**H**), 6.70 (1H, s, aromatic C**H**), 6.68 (1H, s, aromatic C**H**), 5.45 (1H, ddt, *J*=17.0, 10.1, 7.5 Hz, CH_2=C**H**), 5.13–4.94 (2H, m, C**H**$_2$=CH), 5.03 (1H, d, *J*=16.3 Hz, NC**H**H), 4.82 (1H, d, *J*=16.3

Hz, NCH**H**), 3.85 (3H, s, COOC**H**$_3$), 3.70 (3H, s, OC**H**$_3$), 3.67 (3H, s, OC**H**$_3$), 3.09–3.06 (2H, m, CH_2=CHC**H**$_2$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 174.1 (**C**=O), 169.7 (**C**=O), 150.2 (**C**), 149.4 (**C**), 143.3 (**C**), 131.2 (**C**H), 129.9 (**C**), 129.5 (**C**H), 127.5 (**C**), 123.8 (**C**H), 123.3 (**C**H), 121.9 (**C**H), 120.3 (**C**H_2), 111.0 (**C**H), 110.2 (**C**H), 86.1 (**C**-I), 59.7 (**C**), 56.5 (O**C**H_3), 56.2 (O**C**H_3), 53.4 (COO**C**H_3), 48.9 (**C**H_2), 38.3 (**C**H_2).

ESMS: *m/z* (%): 530 $[M+Na]^+$ (100), 508 $[M+H]^+$ (5).

HRMS (ES +ve): $C_{22}H_{22}INNaO_5$ $[M+Na]^+$ 530.0435, found 530.0428.

Data for **276**.

Novel

IR (ATR / golden gate): 3322 (m), 2974 (w), 2933 (w), 2905 (w), 2840 (w), 2128 (w), 1704 (s), 1618 (m), 1503 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 8.99 (1H, s, N**H**), 7.24 (1H, d, *J*=7.6 Hz, aromatic C**H**), 7.15 (1H, app. td, *J*=7.5, 1.0 Hz, aromatic C**H**), 7.06 (1H, s, aromatic C**H**), 6.99 (1H, app. td, *J*=7.5, 1.0 Hz, aromatic C**H**), 6.81 (1H, d, *J*=7.6 Hz, aromatic C**H**), 6.52 (1H, s, aromatic C**H**), 5.41 (1H, m, C**H**=CH_2), 5.03 (1H, dd, *J*=17.0, 1.8 Hz, CH=C**H**H), 4.92 (1H, dd, *J*=10.1, 1.8 Hz, CH=CH**H**), 3.72 (3H, s, OC**H**$_3$), 3.55 (3H, s, OC**H**$_3$), 3.30–3.36 (2H, m, C**H**$_2$Ar), 2.64–2.82 (2H, m, C**H**$_2$CH=CH_2).

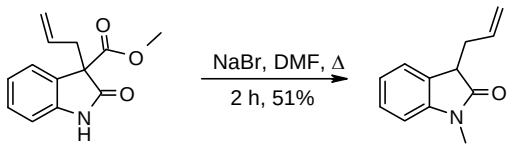
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 181.7 (**C**=O), 148.7 (**C**), 148.1 (**C**), 141.1 (**C**), 132.1 (**C**H), 131.9 (**C**), 131.1 (**C**), 128.1 (**C**H), 125.2 (**C**H), 122.1 (**C**H), 121.6 (**C**H), 119.3 (**C**H_2), 112.5 (**C**H), 109.9 (**C**H), 90.5 (**C**I), 56.0 (O**C**H_3), 55.5 (O**C**H_3), 54.9 (**C**), 45.7 (**C**H_2), 41.9 (**C**H_2).

ESMS: *m/z* (%): 472 $[M+Na]^+$ (472), 921$[M_2+Na]^+$ (100).

HRMS (ES +ve): $C_{20}H_{20}INNaO_3$ $[M+Na]^+$ 472.0380, found 472.0372.

3-Allyl-1-methyl-1,3-dihydro-indol-2-one (281).



266
$C_{13}H_{13}NO_3$
(231.25)

281
$C_{12}H_{13}NO$
(187.24)

A solution of ester **266** (2.16 mmol, 0.50 g) and NaBr (4.32 mmol, 0.45 g) in DMF (100 mL), was heated at reflux for 2 h under nitrogen. Once cool the reaction mixture was diluted with water (100 mL) and extracted with diethyl ether (3 x 60 mL). The organic phases were combined, washed with water (4 x 50 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by column chromatography (silica, 20% diethyl ether in petroleum ether) to give **281** (1.09 mmol, 0.20 g, 51%) as colourless clear oil. Data consistent with the literature.[68]

IR (ATR / golden gate): 3383 (w), 3054 (w), 2979 (w), 2937 (w), 2915 (w), 1701 (s), 1611 (s), 1493 (m), 1469 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

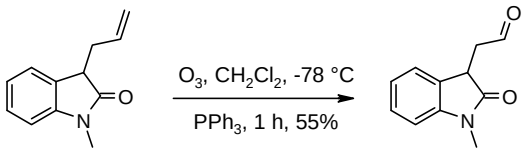
δ ppm 7.23–7.31 (2H, m, 2 x aromatic C**H**), 7.03 (1H, app. td, *J*=7.5, 0.9 Hz, aromatic C**H**), 6.82 (1H, dd, *J*=8.1, 0.6 Hz, aromatic C**H**), 5.76 (1H, dddd, *J*=17.0, 10.1, 7.9, 6.1 Hz, $CH_2C\mathbf{H}=CH_2$), 5.00–5.15 (2H, m, $CH_2CH=C\mathbf{H}_2$), 3.48 (1H, dd, *J*=7.6, 4.9 Hz, ArC**H**), 3.20 (3H, s, $NC\mathbf{H}_3$), 2.83 (1H, m, $C\mathbf{H}HCH=CH_2$), 2.55 (1H, m, $CH\mathbf{H}CH=CH_2$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 177.3 (**C**=O), 144.5 (**C**), 134.3 (**C**H), 128.8 (**C**), 128.1 (**C**H), 124.3 (**C**H), 122.4 (**C**H), 118.0 ($\mathbf{C}H_2$), 108.0 (**C**H), 45.3 ($N\mathbf{C}H_3$), 35.1 ($\mathbf{C}H_2$), 26.3 (**C**H).

ESMS: *m/z* (%): 188 $[M+H]^+$ (100), 210 $[M+Na]^+$ (80).

(1-Methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-acetaldehyde (282).



281
$C_{12}H_{13}NO$
(187.24)

282
$C_{11}H_{11}NO_2$
(189.22)

A flow of 1–2% O_3 in O_2 was bubbled through a solution of alkene **281** (1.09 mmol, 0.20 g) in anhydrous DCM (25 mL) at −78 °C for 30 min where a blue solution persisted. The mixture was then purged with O_2 for 1 h when the blue colour had faded, then PPh_3 (2.73 mmol, 0.72 g) added. After warming to room temperature, the mixture was tested for peroxides with starch-iodide paper then concentrated *in vacuo* and purified by column chromatography (silica, 25% diethyl ether in petroleum ether) to give aldehyde **282** (0.60 mmol, 0.11 g, 55%) as a colourless oil. The aldehyde was analyzed by NMR and used immediately in the subsequent reaction.

Novel

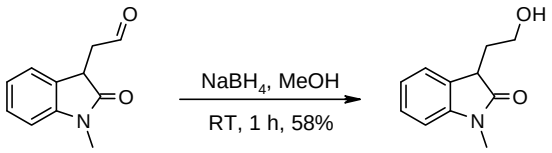
^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 9.89 (1H, t, *J*=0.8 Hz, CH_2CHO), 7.30 (1H, app. td, *J*=7.8, 1.0 Hz, aromatic C**H**), 7.21 (1H, dd, *J*=7.5, 0.6 Hz, aromatic C**H**), 7.03 (1H, app. td, *J*=7.5, 1.0 Hz, aromatic C**H**), 6.85 (1H, d, *J*=7.8 Hz, aromatic C**H**), 3.91 (1H, dd, *J*=8.5, 4.0 Hz, C**H**CH_2CHO), 3.24 (3H, s, NC**H**$_3$), 3.25 (1H, ddd, *J*=18.7, 4.0, 0.8 Hz, C**H**HCHO), 2.88 (1H, ddd, *J*=18.7, 8.5, 0.8 Hz, CH**H**CHO).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 199.1 (**C**HO), 177.0 (**C**=O), 144.4 (**C**), 128.5 (**C**H), 128.4 (**C**), 124.4 (**C**H), 122.8 (**C**H), 108.3 (**C**H), 44.9 (**C**H_2), 40.0 (N**C**H_3), 26.5 (**C**H).

3-(2-Hydroxy-ethyl)-1-methyl-1,3-dihydro-indol-2-one (283).



282
$C_{11}H_{11}NO_2$
(189.22)

283
$C_{11}H_{13}NO_2$
(191.23)

To a solution of aldehyde **282** (0.53 mmol, 0.10 g) in anhydrous MeOH (10 mL) at 0 °C under nitrogen was added $NaBH_4$ (0.58 mmol, 22 mg). The reaction mixture was allowed to warm to room temperature, stirred for 1 h then water (20 mL) was added. The aqueous phase was separated and extracted with ether (3 x 20 mL) then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give alcohol **283** (0.31 mmol, 59 mg, 58%) as a colourless oil, without need for purification. Data consistent with the literature.[69]

IR (ATR / golden gate): 3383 (m), 3060 (w), 2921 (w), 2884 (w), 1685 (s), 1610 (s), 1493 (m), 1469 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

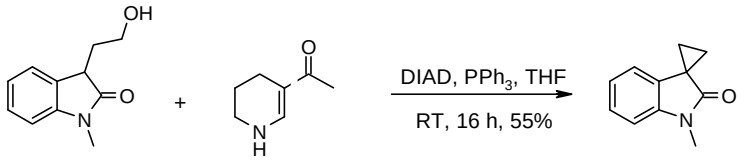
δ ppm 7.31 (1H, app. td, *J*=7.9, 1.0 Hz, aromatic C**H**), 7.26 (1H, dd, *J*=7.9, 0.9 Hz, aromatic C**H**), 7.08 (1H, app. td, *J*=7.7, 0.9 Hz, aromatic C**H**), 6.84 (1H, d, *J*=7.7 Hz, aromatic C**H**), 3.92 (2H, t, *J*=5.8 Hz, C**H**$_2$OH), 3.60 (1H, dd, *J*=8.8, 5.2 Hz, ArC**H**), 3.22 (3H, s, NC**H**$_3$), 2.22 (1H, m, C**H**HCH$_2$OH), 2.03 (1H, m, CH**H**CH$_2$OH).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 179.0 (**C**=O), 144.3 (**C**), 129.1 (**C**), 128.3 (**C**H), 123.8 (**C**H), 122.9 (**C**H), 108.4 (**C**H), 61.2 (**C**H$_2$), 44.7 (N**C**H$_3$), 33.6 (**C**H$_2$), 26.5 (**C**H).

ESMS: *m/z* (%): 214 $[M+Na]^+$ (50), 230 $[M+K]^+$ (100).

1′-Methyl-spiro[cyclopropane-1,3′-indol-2′-one] (285).



283
$C_{11}H_{13}NO_2$
(191.23)

284
$C_7H_{11}NO$
(125.17)

285
$C_{11}H_{11}NO$
(173.22)

To a solution of alcohol **283** (0.21 mmol, 40 mg) and amine **284** (0.23 mmol, 29 mg), in anhydrous THF (10 mL) at 0 °C under nitrogen was added PPh_3 (0.21 mmol, 55 mg) and DIAD (0.21 mmol, 41 μL). The reaction mixture was allowed to warm to room temperature, stirred for 16 h under nitrogen then filtered through silica and concentrated *in vacuo*. Purification by column chromatography (silica, 20→75% diethyl ether in petroleum ether) gave cyclopropane **285** (0.12 mmol, 20 mg, 55%) as a colourless oil. Data consistent with the literature.[70]

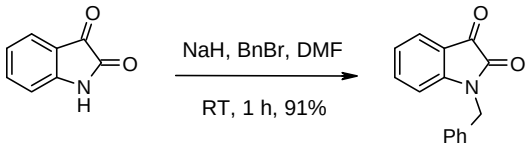
^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.27 (1H, ddd, *J*=7.9, 7.6, 1.2 Hz, aromatic C**H**), 7.03 (1H, app. td, *J*=7.6, 1.0 Hz, aromatic C**H**), 6.91 (1H, d, *J*=7.9 Hz, aromatic C**H**), 6.85 (1H, dd, *J*=7.6, 0.6 Hz, aromatic C**H**), 3.31 (3H, s, NC**H**$_3$), 1.75 (2H, dd, *J*=7.9, 4.3 Hz, -C**H**HC**H**H-), 1.49–1.5 (2H, m, CH**H**CH**H**-).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 177.2 (**C**=O), 143.8 (**C**), 131.1 (**C**), 126.9 (**C**H), 122.1 (**C**H), 118.4 (**C**H), 108.1 (**C**H), 27.2 (**C**), 26.7 (N**C**H$_3$), 19.3 (2x**C**H$_2$).

1-Benzyl-1*H*-indole-2,3-dione (294).



293
$C_8H_5NO_2$
(147.13)

294
$C_{15}H_{11}NO_2$
(237.26)

To a solution if isatin **293** (54.4 mmol, 8.00 g) in anhydrous DMF (200 mL) under nitrogen at 0 ºC was added sodium hydride (60% in mineral oil, 59.8 mmol, 2.40 g) portion-wise. The resulting dark purple reaction mixture was allowed to warm to room temperature and after 30 min benzyl bromide (59.8 mmol, 7.11 mL) was added. After a further 1 h the orange reaction mixture was added cold water (500 mL) and the extracted with DCM (3 x 150 mL). The combined organic phases were washed with brine (500 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give *N*-benzyl isatin (**294**) as an orange solid (49.7 mmol, 11.78 g, 91%). Data consistent with the literature.[71]

Mpt: 127-128 °C (Et_2O) (Lit.[71] 126-127 °C).

IR (ATR / golden gate): 2958 (w), 2917 (w), 2852 (w), 2840 (w), 1731 (s), 1608 (s).

^{1}H NMR (400 MHz, CHLOROFORM-*d*)

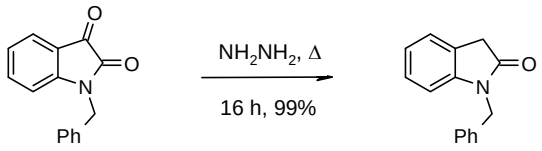
δ ppm 7.54 (1H, dd, *J*=7.5, 1.3 Hz, aromatic C**H**), 7.41 (1H, app. td, *J*=7.8, 1.3 Hz, aromatic C**H**), 7.18–7.33 (5H m, 5 x aromatic C**H**), 7.02 (1H, app. t, *J*=7.5 Hz, aromatic C**H**), 6.71 (1H, d, *J*=7.8 Hz, aromatic C**H**), 4.86 (2H, s, NC**H**$_2$Ph).

^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*)

δ ppm 183.4 (**C**=O), 158.5 (**C**=O), 150.9 (**C**), 138.4 (**C**H), 134.7 (**C**), 129.2 (2x**C**H), 128.3 (**C**H), 127.6 (2x**C**H), 125.6 (**C**H), 124.0 (**C**H), 117.9 (**C**), 111.2 (**C**H), 44.2 (**C**H$_2$).

ESMS: *m/z* (%): 238 $[M+H]^+$ (100), 260 $[M+Na]^+$ (50), 497 $[M_2+Na]^+$ (60).

1-Benzyl-1,3-dihydro-indol-2-one (295).



294
$C_{15}H_{11}NO_2$
(237.26)

295
$C_{15}H_{13}NO$
(223.28)

N-Benzyl isatin (**294**) (25.3 mmol, 6.00 g) was stirred in hydrazine *mono*-hydrate (25 mL) at reflux under nitrogen for 2 h. On cooling to room temperature the reaction mixture was poured onto iced water (100 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the product as a viscous yellow oil (**295**) (25.1 mmol, 5.60 g, 99%). Data consistent with the literature.[72]

IR (ATR / golden gate): 3322 (w), 3060 (w), 3023 (w), 2917 (w), 1701 (s), 1613 (s).

^{1}H NMR (400 MHz, CHLOROFORM-*d*)

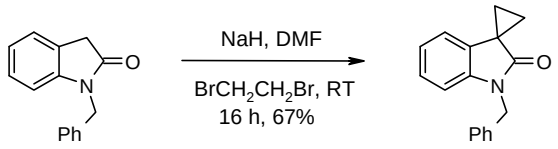
δ ppm 7.18–7.31 (6H, m, 6 x aromatic C**H**), 7.13 (1H, app. t, *J*=7.6 Hz, aromatic C**H**), 6.97 (1H, app. t, *J*=7.2 Hz, aromatic C**H**), 6.69 (1H, d, *J*=7.8 Hz, aromatic C**H**), 4.88 (2H, s, NC**H**$_2$Ph), 3.58 (2H, s, COC**H**$_2$).

^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*)

δ ppm 175.3 (**C**=O), 144.5 (**C**), 136.1 (**C**), 128.9 (2x**C**H), 128.0 (**C**H), 127.7 (**C**H), 127.5 (2x**C**H), 124.6 (**C**), 124.6 (**C**H), 122.5 (**C**H), 109.2 (**C**H), 43.9 (**C**H$_2$), 35.9 (**C**H$_2$).

ESMS: *m/z* (%): 246 $[M+Na]^+$ (100), 224 $[M+H]^+$ (20).

1′-Benzyl-spiro[cyclopropane-1,3′-indol-2′-one] (287).



295
$C_{15}H_{13}NO$
(223.28)

287
$C_{17}H_{15}NO$
(249.32)

To a cooled (0 ºC) solution of oxindole **295** (51.6 mmol, 11.53 g) in anhydrous DMF (250 mL) under nitrogen was added sodium hydride (60% in mineral oil, 113.6 mmol, 4.50 g) portion-wise. The resulting dark red reaction mixture was stirred at room temperature for 1 h then a solution of 1,2-dibromoethane (206.4 mmol, 17.80 mL) in anhydrous DMF (50 mL) was added drop-wise. The reaction mixture was allowed to warm to room temperature and after 18 h was cooled on ice, and quenched with water (300 mL). The aqueous phase was extracted with ethyl acetate (3 x 70 mL) then the combined organic phases were washed with water (4 x 100 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* and purified by column chromatography (silica, 10% ethyl acetate in hexanes) to give the desired compound (**287**) as a white solid (34.7 mmol, 8.64 g, 67%). Data consistent with the literature.[57]

IR (ATR / golden gate): 3056 (w), 3019 (w), 2987 (w), 2921 (w), 1701 (s).

^{1}H NMR (400 MHz, CHLOROFORM-*d*)

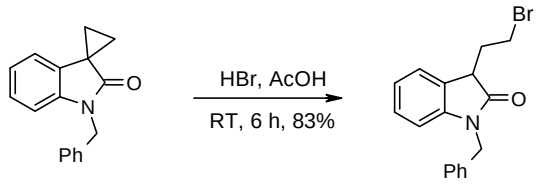
δ ppm 7.17–7.29 (5H, m, 5 x aromatic C**H**), 7.08 (1H, app. t, *J*=7.7 Hz, aromatic C**H**), 6.94 (1H, app. t, *J*=7.4 Hz, aromatic C**H**), 6.79 (1H, d, *J*=7.4 Hz, aromatic C**H**), 6.74 (1H, d, *J*=7.7 Hz, aromatic C**H**), 4.95 (2H, s, NC**H**$_2$Ph), 1.76 (2H, dd, *J*=7.8, 4.0 Hz, -C**H**HC**H**H), 1.51 (2H, dd, *J*=7.8, 4.0 Hz, -CH**H**CH**H**-).

^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*)

δ ppm 177.3 (**C**=O), 142.9 (**C**), 136.4 (**C**), 131.0 (**C**), 128.9 (2x**C**H), 127.7 (**C**H), 127.5 (2x**C**H), 126.8 (**C**H), 122.2 (**C**H), 118.5 (**C**H), 109.2 (**C**H), 44.3 (**C**H$_2$), 27.2 (**C**), 19.6 (2x**C**H$_2$).

ESMS: *m/z* (%): 250 $[M+H]^+$ (100), 272 $[M+Na]^+$ (45).

1-Benzyl-3-(2-bromoethyl)-2,3-dihydro-1*H*-indol-2-one (431).



287
$C_{17}H_{15}NO$
(249.32)

431
$C_{17}H_{16}BrNO$
(330.22)

Cyclopropane **287** (2.19 mmol, 0.55 g) was dissolved in a solution of HBr in acetic acid (30%, 20 mL). After 6 h at room temperature water (40 mL) and ether (40 mL) were added. The aqueous phase was extracted with ether (3 x 40 mL) and the combined organic phases were washed with water (3 x 40 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Azeotropic removal of acetic acid with toluene (3 x 100 mL) gave bromide **431** (1.82 mmol, 0.60 g, 83%) as a colourless oil.

Novel

IR (ATR / golden gate): 3060 (w), 3027 (w), 2917 (w), 1702 (s), 1611 (s), 1487 (s), 1466 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

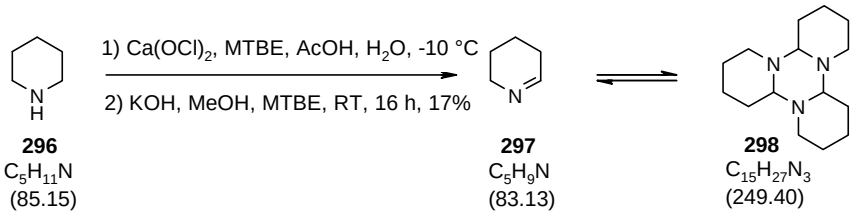
δ ppm 7.19–7.33 (6H, m, 6 x aromatic C**H**), 7.16 (1H, app. td, *J*=7.8, 1.0 Hz, aromatic C**H**), 7.01 (1H, app. td, *J*=7.6, 1.0 Hz, aromatic C**H**), 6.72 (1H, d, *J*=7.8 Hz, aromatic C**H**), 4.88 (2H, s, NC**H**$_2$Ph), 3.67–3.77 (2H, m, CHCH$_2$C**H**$_2$Br), 3.58 (1H, dd, *J*=7.4, 6.5 Hz, C**H**CH$_2$CH$_2$Br), 2.44 (2H, m, CHC**H**$_2$CH$_2$Br).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 177.2 (**C**=O), 143.6 (**C**), 136.0 (**C**), 129.0 (2x**C**H), 128.4 (**C**H), 128.0 (**C**), 127.8 (**C**H), 127.5 (2x**C**H), 124.1 (**C**H), 122.8 (**C**H), 109.4 (**C**H), 44.1 (**C**H), 43.9 (**C**H$_2$), 34.4 (**C**H$_2$), 30.1 (**C**H$_2$).

ESMS: *m/z* (%): 330:332 {1:1} $[M+H]^+$ Br^{79}:Br^{81} (100), 352:354 {1:1} $[M+Na]^+$ Br^{79}:Br^{81} (80).

2,3,4,5-Tetrahydro-pyridine (297) and its cyclic trimer (298).



296
$C_5H_{11}N$
(85.15)

297
C_5H_9N
(83.13)

298
$C_{15}H_{27}N_3$
(249.40)

To a solution of piperidine **296** (47.0 mmol, 4.60 mL) in water (4 mL) was added glacial acetic acid (61.6 mmol, 3.80 mL). The resulting solution was added drop-wise over 10 min to a slurry of calcium hypochlorite (32.4 mmol, 4.64 g) stirred in water (10 mL) and methyl *t*-butyl ether (10 mL) at −10 ºC behind a blast screen. After 30 min the organic phase was separated and added drop-wise to a solution of potassium hydroxide (68.8 mmol, 3.80 g) in methanol (10 mL) 0 ºC. The reaction mixture was allowed to warm to room temperature and after 16 h the precipitate formed was collected by filtration, washed with methanol. The filtrate and combined washings were concentrated *in vacuo* and partitioned between water (100 mL) and ether (80 mL). The aqueous phase was extracted with ether (3 x 80 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting oil was dissolved in acetone (10 mL) and cooled to –20 ºC overnight. The white crystals formed were collected by filtration, washed with cold acetone, and dried under vacuum to give imine **298** (7.82 mmol, 1.95 g, 17%) as its cyclic trimer (a white solid). Data consistent with the literature.[58]

IR (ATR / golden gate): 3215 (w), 2962 (m), 2923 (s), 2844 (m), 2807 (m), 2774 (m), 2713 (m), 2586 (w), 2529 (w).

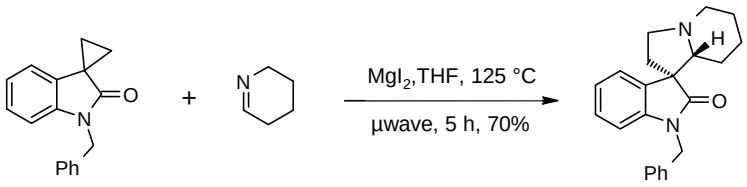
^{1}H NMR (400 MHz, CHLOROFORM-*d*)

δ ppm 3.06–3.19 (3H, m, 3 x NC**H**), 2.73–2.87 (3H, m, 3 x NC**H**H), 1.95–2.09 (3H, m, 3 x NC**H**H), 1.52–1.82 (15H, m, 3 x C**H**$_2$C**H**$_2$C**H**HCH), 1.19–1.40 (3H, m, C**H**$_2$'s in ring).

^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*)

δ ppm 82.2 (**C**H), 46.6 (**C**H$_2$), 29.4 (**C**H$_2$), 26.0 (**C**H$_2$), 22.5 (**C**H$_2$).

1′-Benzyloctahydrospiro[indolizine-1,3′-indol-2′-one] (299).



287
$C_{17}H_{15}NO$
(249.32)

297
C_5H_9N
(83.13)

299
$C_{22}H_{24}N_2O$
(332.45)

Cyclopropane (**287**) (0.40 mmol, 100 mg), imine (**297**) (0.35 mmol, 87 mg) and MgI_2 (0.17 mmol, 47 mg) were dissolved in anhydrous THF (2 mL). The reaction vessel was flushed with nitrogen, heated under microwave irradiation (150 W, 125 °C) for 5 h, then cooled to room temperature. Water (10 mL) was added and the phases separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL), then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 5-10% ethyl acetate in hexanes) to give the desired product (**299**) (0.28 mmol, 93 mg, 70%) as a colourless oil. Data consistent with the literature.[57]

IR (ATR / golden gate): 2958 (w), 2929 (w), 2901 (w), 2848 (w), 2803 (w), 2770 (w), 2721 (w), 1698 (s), 1609 (m).

^{1}H NMR (400 MHz, CHLOROFORM-*d*)

δ ppm 7.45 (1H, d, *J*=7.4 Hz, aromatic C**H**), 7.22–7.35 (5H, m, 5 x aromatic C**H**), 7.13 (1H, app. td, *J*=7.8, 1.0 Hz, aromatic C**H**), 7.02 (1H, app. td, *J*=7.4, 1.0 Hz, aromatic C**H**), 6.70 (1H, d, *J*=7.8 Hz, aromatic C**H**), 5.05 (1H, d, *J*=15.7 Hz, NC**H**HPh), 4.80 (1H, d, *J*=15.7 Hz, NCH**H**Ph), 3.31 (1H, td, *J*=8.6, 2.2 Hz, NC**H**H), 3.21 (1H, d, *J*=10.8 Hz, NCH**H**), 2.36–2.51 (3H, m, NC**H**+NC**H**H+NCH**H**), 1.98–2.15 (2H, m, 2xC**H**H), 1.57–1.72 (2H, m, 2xC**H**H), 1.47 (1H, dddd, *J*=12.8, 12.7, 12.7, 4.1, Hz, CH**H**), 1.09–1.25 (2H, m, 2xCH**H**), 0.90 (1H, qd, *J*=12.8, 3.5 Hz, CH**H**).

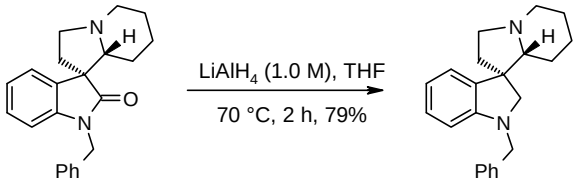
^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*)

δ ppm 180.0 (**C**=O), 142.4 (**C**), 136.3 (**C**), 133.9 (**C**), 128.9 (2x**C**H), 127.7 (**C**H), 127.5 (2x**C**H), 127.3 (**C**H), 125.1 (**C**H), 122.5 (**C**H), 108.8 (**C**H), 72.3 (**C**H), 56.8 (**C**), 54.4 (**C**H_2), 53.8 (**C**H_2), 44.0 (**C**H_2), 35.1 (**C**H_2), 26.6 (**C**H_2), 25.4 (**C**H_2), 23.9 (**C**H_2).

^{1}H-^{1}H and ^{1}H-^{13}C correlations obtained to confirm above NMR assignments.

ESMS: *m/z* (%): 333 $[M+H]^+$ (90), 355 $[M+Na]^+$ (30), 688 $[M_2+Na]^+$ (100).

1′-Benzyl-2,2′,3,3′,4,5,6,7,8,8a-decahydrospiro[indolizine-1,3′-indole] (300).



299
$C_{22}H_{24}N_2O$
(332.45)

300
$C_{22}H_{26}N_2$
(318.47)

To a solution of oxindole **299** (0.27 mmol, 90 mg) in anhydrous THF (20 mL) at room temperature, under nitrogen, was added a solution of $LiAlH_4$ (1.0 M in THF, 0.81 mmol, 0.81 mL) drop-wise. The reaction mixture was stirred at room temperature for 30 min, heated to 70 °C for 2 h, then cooled to 0 °C. Water (30 mL) was added carefully then the reaction mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by column chromatography (silica, 1% MeOH in $CHCl_3$) to give **300** (0.21 mmol, 68 mg, 79%) as a brown oil.

Novel

IR (ATR / golden gate): 3066 (w), 3032 (w), 3002 (w), 2926 (w), 2854 (w), 2778 (w), 1603 (m), 1486 (m), 1452 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.24–7.37 (6H, m, 6 x aromatic C**H**), 7.08 (1H, app. td, *J*=7.7, 1.2 Hz, aromatic C**H**), 6.72 (1H, app. t, *J*=7.4 Hz, aromatic C**H**), 6.50 (1H, d, *J*=7.8 Hz, aromatic C**H**), 4.33 (1H, d, *J*=14.8 Hz, NC**H**HPh), 4.16 (1H, d, *J*=14.8 Hz, NCH**H**Ph), 3.30 (1H, d, *J*=9.0 Hz, NC**H**H), 3.23 (1H, d, *J*=9.0 Hz, NCH**H**), 3.11–3.20 (2H, m, 2xNC**H**H), 2.10–2.27 (2H, m, 2xNC**H**H), 1.64–2.04 (3H, m, 2xCH**H** and NC**H**), 1.40–1.63 (2H, m, 2xCH**H**), 0.82–1.23 (4H, m, 4xCH**H**).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 152.2 (**C**), 138.8 (**C**), 128.7 (2x**C**H), 128.0 (2x**C**H), 127.7 (**C**H), 127.2 (**C**H), 125.2 (**C**H), 118.0

(**C**H), 107.0 (**C**H), 74.6 (N**C**H), 65.8 (N**C**H_2), 54.3 (N**C**H_2), 54.0 (N**C**H_2), 53.7 (N**C**H_2Ph), 52.5 (**C**), 38.3 (**C**H_2), 26.6 (**C**H_2), 25.4 (**C**H_2), 24.4 (**C**H_2).

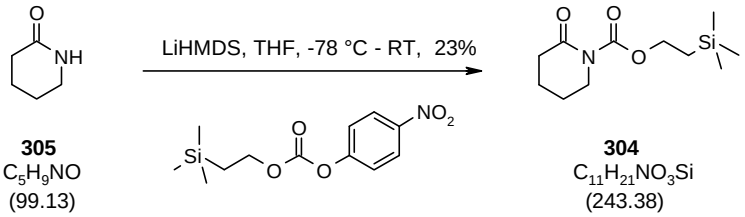
NB. 1 (**C**) not observed.

^{1}H-^{1}H and ^{1}H-^{13}C correlations obtained to confirm above NMR assignments.

ESMS: *m/z* (%): 319 $[M+H]^+$ (100).

Synthetic Procedures–Chapter 3

2-(Trimethylsilyl)ethyl 2-oxo-piperid-1-yl carbonate (304).



305
C_5H_9NO
(99.13)

304
$C_{11}H_{21}NO_3Si$
(243.38)

To a solution of LiHMDS (2.55 mmol, 1.20 mL) in anhydrous THF (10 mL) under argon at −78 °C was added *n*-BuLi (2.2 M, 5.55 mmol, 1.20 mL). The reaction mixture was warmed to 0 °C and stirred for 30 min before being cooled to −78 °C. A solution of δ-valerolactam (**305**) (5.00 mmol, 0.50 g) in anhydrous THF (6 mL) was added drop-wise and the solution stirred at −78 °C for 30 min. 2-(Trimethylsilyl)ethyl 4-nitrophenyl carbonate (5.00 mmol, 1.43 g) in anhydrous THF (10 mL) was added and the reaction mixture was allowed to warm to room temperature overnight. Water (100 mL) was added and the reaction mixture extracted with ethyl acetate (3 x 100 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **304** (1.16 mmol, 0.28 g, 23% crude) as a colourless oil.

Novel

IR (ATR / golden gate): 2945 (m), 2892 (w), 1733 (m), 1709 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 4.29–4.36 (2H, m, OC**H**$_2$CH$_2$Si(CH$_3$)$_3$), 3.71 (2H, t, *J*=6.2 Hz, NC**H**$_2$CH$_2$CH$_2$CH$_2$), 2.49–2.56 (2H, m, NCH$_2$CH$_2$CH$_2$C**H**$_2$), 1.78–1.86 (4H, m, NCH$_2$C**H**$_2$C**H**$_2$CH$_2$), 1.07–1.14 (2H, m, OCH$_2$C**H**$_2$Si(CH$_3$)$_3$), 0.04 (9 H, s, OCH$_2$CH$_2$Si(C**H**$_3$)$_3$).

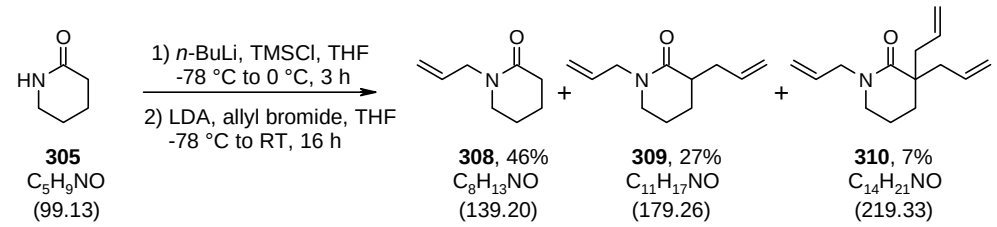
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 171.4 (**C**=O), 154.6 (**C**=O), 65.7 (**C**H$_2$), 46.5 (**C**H$_2$), 35.0 (**C**H$_2$), 22.9 (**C**H$_2$), 20.6 (**C**H$_2$), 17.7 (**C**H$_2$), −1.4 (3 x **C**H$_3$).

ESMS: *m/z* (%): 509 $[M_2+Na]^+$ (100), 266 $[M+Na]^+$ (20).

HRMS (ES +ve): $C_{11}H_{21}NNaO_3Si$ $[M+Na]^+$ 266.1188, found 266.1183.

1-Allyl-piperidin-2-one (308), 1,3-diallyl-piperidin-2-one (309) and 1,3,3-triallyl-piperidin-2-one (310).



To a solution of δ–valerolactam **305** (5.04 mmol, 0.50 g) in anhydrous THF (30 mL) under nitrogen at −78°C, was added a solution of *n*-BuLi (1.6 M in hexanes, 5.09 mmol, 3.18 mL). The reaction mixture was warmed to 0 °C over 1 h, then trimethylsilyl chloride (5.54 mmol, 0.70 mL) was added. After 2 h LDA (2.0 M in THF, 15.12 mmol, 7.60 mL) was added, and the resulting red solution stirred for 1 h then cooled to −78°C. Allyl bromide (60.48 mmol, 5.20 mL) was added drop-wise and the reaction mixture allowed to slowly warm to room temperature. After 16 h a saturated solution of NH_4Cl (50 mL) was added and the mixture extracted with DCM (3 x 50 mL). The combined organic phases were washed with HCl (1 M, 100 mL), water (100 mL) and brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 20% ethyl acetate in hexanes) to give firstly **308** (2.32 mmol, 0.32 g, 46%), then **309** (1.37 mmol, 0.25 g, 27%) and finally **310** (0.36 mmol, 78 mg, 7%) each as colourless oils.

Data for **308** consistent with the literature.[73]

IR (ATR / golden gate): 3079 (w), 3013 (w), 2928 (w), 2855 (w), 1631 (s), 1470 (w).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 5.76 (1H, ddt, *J*=16.7, 10.6, 6.0 Hz, $NCH_2C\mathbf{H}=CH_2$), 5.21–4.99 (2H, m, $NCH_2CH=C\mathbf{H}_2$), 4.00 (2H, m, $NC\mathbf{H}_2CH=CH_2$), 3.28–3.20 (2H, m, $NC\mathbf{H}_2CH_2CH_2CH_2$), 2.45–2.36 (2H, m, $NCH_2CH_2CH_2C\mathbf{H}_2$), 1.78–1.85 (4H, m, $NCH_2C\mathbf{H}_2C\mathbf{H}_2CH_2$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 169.6 (**C**=O), 132.9 (**C**H=CH_2), 117.1 (CH=**C**H_2), 49.3 (**C**H_2), 47.2 (**C**H_2), 32.3 (**C**H_2), 23.2 (**C**H_2), 21.4 (**C**H_2).

Data for **309.**

Novel

IR (ATR / golden gate): 3452 (w), 3081 (w), 2974 (w), 2933 (w), 2860 (w), 1634 (s), 1491 (m), 1462 (m), 1442 (m), 1413 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 5.85–5.69 (2H, m, 2 x C**H**=CH_2), 5.20–5.01 (4H, m, 2 x CH=C**H**$_2$), 4.06-3.91 (2H, m, NC**H**$_2$CH=CH_2), 3.27-3.18 (2H, m, NC**H**$_2$$CH_2$$CH_2$), 2.67 (1H, m, C**H**$CH_2$CH=$CH_2$), 2.40 (1H, m, CHC**H**HCH=CH_2), 2.28 (1H, m, CHCH**H**CH=CH_2), 1.97–1.82 (2H, m, 2 x C**H**H), 1.74 (1H, m, CH**H**), 1.57 (1H, m, C**H**H).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 171.8 (**C**=O), 136.7 (**C**H), 133.2 (**C**H), 117.1 (**C**H_2), 116.9 (**C**H_2), 49.8 (**C**H_2), 47.7 (**C**H_2), 41.4 (**C**H), 36.6 (**C**H_2), 26.3 (**C**H_2), 21.9 (**C**H_2).

ESMS: *m/z* (%): 202 $[M+Na]^+$ (100), 381 $[M_2+Na]^+$ (20).

Data for **310.**

Novel

IR (ATR / golden gate): 3077 (w), 3013 (w), 2975 (w), 2930 (m), 2850 (w), 1631 (s), 1488 (m), 1439 (m), 1415 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 5.83–5.66 (3H, m, NCH_2C**H**=CH_2 and 2 x CH_2C**H**=CH_2), 5.19–5.00 (6H, m, NCH_2CH=C**H**$_2$ and 2 x CH_2CH=C**H**$_2$), 3.97 (2H, dd, *J*=5.9, 1.4 Hz, NC**H**$_2$CH=CH_2), 3.20 (2H, t, *J*=5.6 Hz, NC**H**$_2$$CH_2$$CH_2$), 2.60-2.50 (2H, m, 2 x C**H**HCH=CH_2),

2.12–2.23 (2H, m, 2 x CH**H**CH=CH_2), 1.69–1.84 (4H, m, $NCH_2C\mathbf{H}_2C\mathbf{H}_2$).

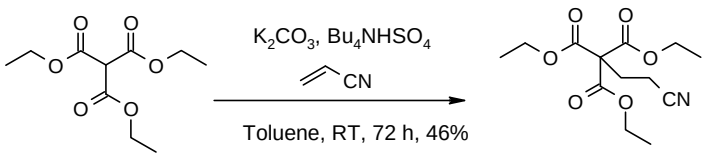
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 173.7 (**C**=O), 134.8 (2x**C**H), 133.3 (**C**H), 118.1 (2x$\mathbf{C}H_2$), 117.0 ($\mathbf{C}H_2$), 50.1 ($\mathbf{C}H_2$), 47.9 ($\mathbf{C}H_2$), 45.0 (**C**), 43.5 (2x$\mathbf{C}H_2$), 29.3 ($\mathbf{C}H_2$), 19.8 ($\mathbf{C}H_2$).

ESMS: *m/z* (%): 220 $[M+H]^+$ (30), 242 $[M+Na]^+$ (100), 462 $[M_2+Na]^+$ (50).

HRMS (EI): $C_{14}H_{21}NO$ $[M]^{+\cdot}$ 219.1618, found 219.1619.

Diethyl 2-(2-cyano-ethyl)-2-ethoxycarbonyl-malonate (314).



315
$C_{10}H_{16}O_6$
(232.24)

314
$C_{13}H_{19}NO_6$
(285.30)

To a mixture of triethyl methanetricarboxylate (**315**) (16.00 mmol, 3.4 mL) in toluene (3 mL) at room temperature was added acrylonitrile (14.00 mmol, 0.9 mL), K_2CO_3 (4.20 mmol, 0.58 g) and Bu_4NHSO_4 (0.70 mmol, 0.24 g). After 24 h the reaction mixture was washed with water (20 mL) and the aqueous phase extracted with ether (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 20% diethyl ether in petroleum ether) to give the desired compound (**314**) as a yellow oil (6.49 mmol, 1.93 g, 46%). Data consistent with the literature.[60]

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

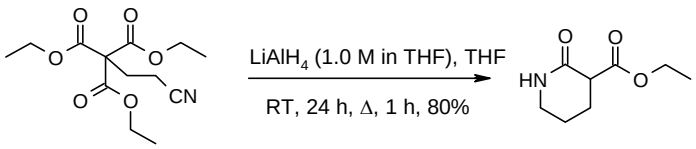
δ ppm 4.26 (6H, q, *J*=7.1 Hz, 3 x $COOC\mathbf{H}_2CH_3$), 2.72–2.63 (2H, m, $CH_2C\mathbf{H}_2CN$), 2.53–2.44 (2H, m, $C\mathbf{H}_2CH_2CN$), 1.27 (9H, t, *J*=7.1 Hz, 3 x $COOCH_2C\mathbf{H}_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 166.1 (3x**C**=O), 118.9 (**C**N), 64.3 (**C**), 62.8 (3x$\mathbf{C}H_2$), 28.9 ($\mathbf{C}H_2$), 13.9 (3x$\mathbf{C}H_3$), 13.5 ($\mathbf{C}H_2$).

ESMS: *m/z* (%): 308 $[M+Na]^+$ (100).

Ethyl 2-oxo-piperidine-3-carboxylate (320).



314
$C_{13}H_{19}NO_6$
(285.30)

320
$C_8H_{13}NO_3$
(171.20)

To anhydrous THF (20 mL) under argon at 0 °C was added $LiAlH_4$ (1.0 M in THF, 2.35 mmol, 2.4 mL) drop-wise. To this was added a solution of nitrile (**314**) (0.47 mmol, 0.14 g) in anhydrous THF (2 mL). After 24 h at room temperature the reaction mixture was heated to reflux for 1 h then cooled to room temperature and water (10 mL) added carefully. The aqueous phase was extracted with ether (3 x 30 mL) then continuously extracted for 16 h with hot ethyl acetate (80 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (**320**) (0.37 mmol, 64 mg, 80%) as a yellow oil. Data consistent with the literature.[60]

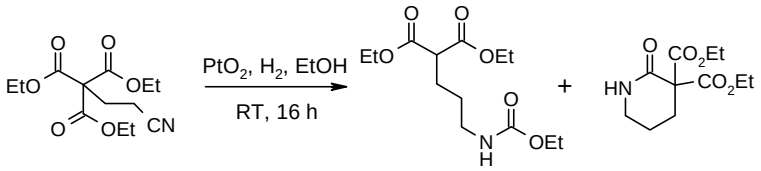
IR (ATR / golden gate): 3304 (w), 3225 (w), 2941 (w), 2873 (w), 1731 (s), 1655 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):
δ ppm 6.56 (1H, b s, N**H**), 4.22 (2H, m, $CO_2C\mathbf{H}_2CH_3$), 3.43–3.28 (3H, m, C**H**$CH_2CH_2C\mathbf{H}_2N$), 2.17–2.01 (2H, m, 2xC**H**H), 1.93 (1H, m, CH**H**), 1.75 (1H, m, CH**H**), 1.29 (3H, t, *J*=7.1 Hz, $CO_2CH_2C\mathbf{H}_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)
δ ppm 170.9 (**C**=O), 168.3 (**C**=O), 61.6 (**C**H_2), 48.8 (**C**H), 42.4 (**C**H_2), 25.0 (**C**H_2), 20.5 (**C**H_2), 14.3 (**C**H_3).

ESMS: *m/z* (%): 194 $[M+Na]^+$ (100).

Diethyl 2-(3-ethoxycarbonylamino-propyl)-malonate (322) and diethyl 2-oxo-piperidine-3,3-dicarboxylate (312).



315
$C_{13}H_{19}NO_6$
(285.30)

322, 36%
$C_{13}H_{23}NO_6$
(289.33)

312, 17%
$C_{11}H_{17}NO_5$
(243.26)

To a solution of nitrile (**315**) (0.70 mmol, 0.20 g) in EtOH (5 mL) was added Adams' catalyst (PtO_2, 0.07 mmol, 16 mg). The reaction flask was evacuated and refilled with argon (x3) before being evacuated and refilled with hydrogen (x3). The reaction mixture was stirred under a hydrogen atmosphere (balloon) at room temperature for 16 h before being filtered through Celite® and washed with ethanol. The filtrate was concentrated *in vacuo* and purified by column chromatography (silica, 20→50% ethyl acetate in hexanes then 1–5% MeOH in ethyl acetate) to give firstly **322** (0.25 mmol, 73 mg, 36%) as a clear oil then lactam (**312**) (0.19 mmol, 29 mg, 17%) as a cream solid.

Data for **322**

Novel

IR (ATR / golden gate): 3387 (w), 3330 (w), 2979 (w), 2933 (w), 2907 (w), 2862 (w), 1720 (s), 1693 (s), 1526 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 4.81 (1H, b s, N**H**), 4.16 (4H, q, *J*=7.2 Hz, 2xCOOC**H**$_2$CH$_3$), 4.07 (2H, q, *J*=6.6 Hz, NHCOOC**H**$_2$CH$_3$), 3.30 (1H, t, *J*=7.5 Hz, C**H**CH$_2$CH$_2$CH$_2$NH), 3.16 (2H, app. q, *J*=5.9 Hz, CHCH$_2$CH$_2$C**H**$_2$NH), 1.89 (2H, m, 2 x C**H**H), 1.57–1.47 (2H, m, 2 x CH**H**), 1.23 (6H, t, *J*=7.2 Hz, 2 x COOCH$_2$C**H**$_3$), 1.19 (3H, t, *J*=6.6 Hz, NHCOOCH$_2$C**H**$_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 169.4 (2x**C**=O), 156.8 (**C**=O), 61.5 (2xO**C**$H_2$$CH_3$), 60.8 (O**C**$H_2$$CH_3$), 51.7 (**C**H), 40.5 (**C**H_2), 27.8 (**C**H_2), 25.9 (**C**H_2), 14.7 (OCH_2**C**H_3), 14.2 (2xOCH_2**C**H_3).

ESMS: *m/z* (%): 312 $[M+Na]^+$ (100).

HRMS (ES +ve): $C_{13}H_{23}NNaO_6$ $[M+Na]^+$ 312.1423, found 312.1418.

Data for **312** consistent with the literature.[60]

IR (ATR / golden gate): 3194 (w), 3073 (w), 2971 (w), 2945 (w), 2899 (w), 1746 (m), 1724 (s), 1675 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

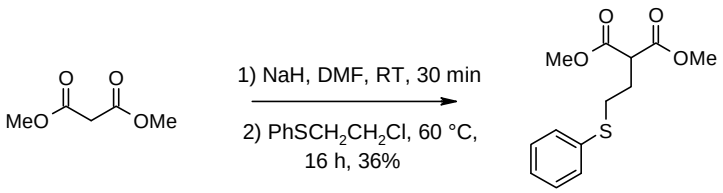
δ ppm 6.51 (1H, b s, N**H**), 4.28 (4H, q, *J*=7.1 Hz, 2 x COOC**H**$_2$$CH_3$), 3.36 (2H, td, *J*=6.3, 2.1 Hz, NHC**H**$_2$$CH_2CH_2$), 2.48–2.42 (2H, m, 2 x C**H**H), 1.82–1.73 (2H, m, 2 x CH**H**), 1.30 (6H, t, *J*=7.1 Hz, 2 x COOCH_2C**H**$_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 168.1 (2x**C**=O), 166.0 (**C**=O), 63.5 (**C**), 62.5 (2xO**C**$H_2$$CH_3$), 42.2 (**C**$H_2$), 28.7 (**C**$H_2$), 19.0 (**C**$H_2$), 14.1 (2xOC$H_2$**C**$H_3$).

ESMS: *m/z* (%): 266 $[M+Na]^+$ (40), 509 $[M_2+Na]^+$ (100).

Dimethyl 2-(2-phenylsulfonyl-ethyl)-malonate (327).



326
$C_5H_8O_4$
(132.12)

327
$C_{13}H_{16}O_4S$
(268.33)

To a solution of dimethyl malonate (**326**) (2.27 mmol, 0.26 mL) in anhydrous DMF (10 mL) at 0 °C under argon was added sodium hydride (60% in mineral oil, 5.68 mmol, 0.23 g). The reaction mixture was allowed to warm to room temperature and after 30 min 2-chloroethyl phenyl sulfide (5.68 mmol, 0.84 mL) was added dropwise. After 6 h at room temperature the temperature was raised to 60 °C for 16 h then reduced to room temperature. Water (20 mL) was added and the reaction mixture extracted with ether (3 x 20 mL). The combined organic phases were washed with water (4 x 20 mL) and brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 5% diethyl ether in petroleum ether) to give the *mono*-alkylated material **327** (0.82 mmol, 0.22 g, 36%) as a colourless liquid. Data consistent with the literature.[74]

IR (ATR / golden gate): 3002 (w), 2949 (w), 1729 (s), 1436 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

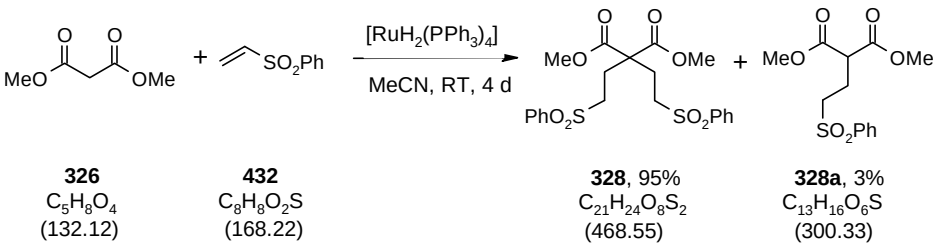
δ ppm 7.39–7.28 (3H, m, 3 x aromatic C**H**), 7.24–7.15 (2H, m, 2 x aromatic C**H**), 3.74 (6H, s, 2 x OC**H**$_3$), 3.66 (1H, t, *J*=7.2 Hz, C**H**CH$_2$CH$_2$SPh), 2.97 (2H, t, *J*=7.2 Hz, CH$_2$C**H**$_2$SPh), 2.26-2.19 (2H, app. q, *J*=7.2 Hz, CHC**H**$_2$CH$_2$SPh).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 169.5 (2x**C**=O), 135.6 (**C**), 129.9 (2x**C**H), 129.2 (2x**C**H), 126.5 (**C**H), 52.8 (2xO**C**H$_3$), 50.4 (**C**H), 31.6 (**C**H$_2$), 28.5 (**C**H$_2$).

ESMS: *m/z* (%): 291 $[M+Na]^+$ (100).

Dimethyl 2,2-*bis*-(2-benzylsulfonyl-ethyl)-malonate (328) and dimethyl 2-(2-benzylsulfonyl-ethyl)-malonate (328a).



326 $C_5H_8O_4$ (132.12)

432 $C_8H_8O_2S$ (168.22)

328, 95% $C_{21}H_{24}O_8S_2$ (468.55)

328a, 3% $C_{13}H_{16}O_6S$ (300.33)

To a solution of dimethyl malonate (**326**) (3.78 mmol, 0.43 mL) in acetonitrile (10 mL) was added phenyl vinyl sulfone (11.40 mmol, 1.90 g) and dihydridotetrakis(triphenylphosphine)-ruthenium(II) (0.11 mmol, 0.13 g). The dark green solution was stirred at room temperature for 4 d, filtered, concentrated *in vacuo* and purified by column chromatography (silica, 30→70% ethyl acetate in hexanes) to give firstly *bis*-alkylated material (**328**) (3.58 mmol, 1.68 g, 95%) then the *mono*-alkylation material (**328a**) (0.11 mmol, 19 mg, 3%), both as a clear oils.

Data for **328** consistent with the literature.[61]

IR (ATR / golden gate): 3002 (w), 3960 (w), 2933 (w), 1731 (s), 1444 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

δ ppm 7.87–7.94 (4H, m, 4 x aromatic C**H**), 7.56–7.74 (6H, m, 6 x aromatic C**H**), 3.67 (6H, s, 2 x OC**H**$_3$), 3.14–3.04 (4H, m, 2 x $CH_2C\mathbf{H}_2SO_2Ph$), 2.27–2.17 (4H, m, 2 x $C\mathbf{H}_2CH_2SO_2Ph$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 169.8 (2x**C**=O), 138.8 (2x**C**), 134.2 (2x**C**H), 129.7 (4x**C**H), 128.2 (4x**C**H), 55.4 (**C**), 53.3 (2xO**C**H$_3$), 51.7 (2x**C**H$_2$), 26.8 (2x**C**H$_2$).

ESMS: *m/z* (%): 491 $[M+Na]^+$ (70), 959 $[M_2+Na]^+$ (100).

Data for **328a** consistent with the literature.[75]

IR (ATR / golden gate): 2956 (w), 2359 (w), 2340 (w), 1730 (s), 1446 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.94–7.88 (2H, m, 2 x aromatic C**H**), 7.71–7.53 (3H, m, 3 x aromatic C**H**), 3.72 (6H, s, 2 x OC**H**$_3$), 3.58 (1H, t, *J*=7.1 Hz, C**H**CH$_2$CH$_2$SO$_2$Ph), 3.27–3.16 (2H, m, CHCH$_2$C**H**$_2$SO$_2$Ph), 2.28 (2H, m, CHC**H**$_2$CH$_2$SO$_2$Ph).

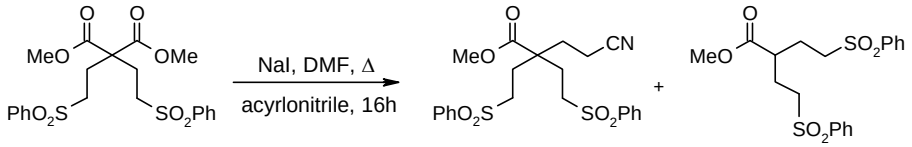
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 168.7 (2x**C**=O), 138.8 (**C**), 134.1 (**C**H), 129.5 (2x**C**H), 128.2 (2x**C**H), 53.5 (**C**H$_2$), 52.9 (2xO**C**H$_3$), 49.5 (**C**H), 22.2 (**C**H$_2$).

ESMS: *m/z* (%): 323 $[M+Na]^+$ (100).

HRMS (ES +ve): $C_{13}H_{16}NaO_6S$ $[M+Na]^+$ 323.05653, found 323.0560.

Methyl 2,2-b*is*-(2-benzylsulfonyl-ethyl)-4-cyano-butyrate (329) and methyl 4-benzenesulfonyl-2-(2-benzenesulfonyl-ethyl)-butyrate (330).



To a solution of malonate (**328**) (0.64 mmol, 0.30 g) in anhydrous DMF (10 mL) at room temperature under argon was added NaI (1.28 mmol, 0.19 g) and acrylonitrile (3.20 mmol, 0.21 mL). The reaction mixture was heated to 130 °C for 16 h, then cooled to room temperature and water (15 mL) added. The reaction mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases washed with water (4 x 10 mL) and brine (20 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 50% ethyl acetate in hexanes) to give an inseparable 1:1 mixture of the desired product **329** and the decarboxylated product **330** (133 mg) as a brown solid.

Novel

IR (ATR / golden gate): 3066 (w), 3020 (w), 2949 (w), 2930 (w), 2253 (w), 1727 (s), 1448 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

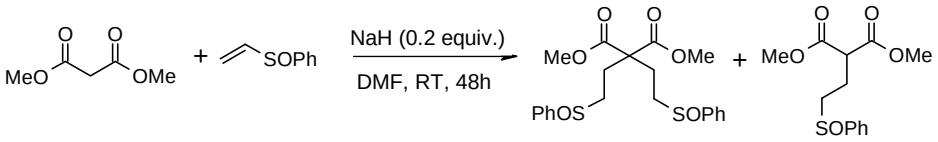
δ ppm 7.93–7.85 (4H+4H, m, 2 x 4 x aromatic C**H**), 7.71–7.64 (2H+2H, m, 2 x 2 x aromatic C**H**), 7.63–7.54 (4H+4H, m, 2 x 4 x aromatic C**H**), 3.63 (3H, s, OC**H**$_3$), 3.62 (3H, s, OC**H**$_3$), 3.12–3.05 (2H+2H, m, 2 x $CH_2C\mathbf{H}_2SO_2Ph$), 3.01-2.94 (2H+2H, m, 2 x $CH_2C\mathbf{H}_2SO_2Ph$), 2.64 (1H, m, C**H**$(CH_2CH_2SO_2Ph)_2$, **330**), 2.22 (2H, t, *J*=7.8 Hz, $CH_2C\mathbf{H}_2CN$, **329**), 2.07-1.84 (4H+4H+2H, m, 4 x $C\mathbf{H}_2CH_2SO_2Ph$ and $C\mathbf{H}_2CH_2CN$ (**329**)).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 173.5 (**C**=O), 173.2 (**C**=O), 138.9 (**C**), 138.6 (**C**), 134.3 (**C**H), 134.1 (**C**H), 129.7 (**C**H), 129.6 (**C**H), 128.1 (**C**H), 128.1 (**C**H), 118.5 (**C**N), 53.7 (**C**H_2), 53.0 (O**C**H_3), 52.3 (O**C**H_3), 51.1 (**C**H_2), 46.8 (**C**), 42.1 (**C**H), 30.8 (**C**H_2), 26.5 (**C**H_2), 24.7 (**C**H_2), 12.5 (**C**H_2).

ESMS: *m/z* (%): 433 [M(**330**)+Na]$^+$ (100), 486 [M(**329**)+Na]$^+$ (40).

Dimethyl 2,2-b*is*-(2-benzenesulfinyl-ethyl)-malonate (332) and dimethyl 2-(2-benzenesulfinyl-ethyl)-malonate (333).



326
$C_5H_8O_4$
(132.12)

433
C_8H_8OS
(152.22)

332, 77%
$C_{21}H_{24}O_6S_2$
(436.55)

333, 9%
$C_{13}H_{16}O_5S$
(284.33)

To a solution of dimethyl malonate (**326**) (6.00 mmol, 0.69 mL) in anhydrous DMF (30 mL) under argon was added NaH (60% dispersion in mineral oil, 1.20 mmol, 48 mg). The reaction mixture was stirred at room temperature for 15 min then phenyl vinyl sulfoxide (**433**) (13.20 mmol, 1.80 mL) added drop-wise. After 48 h water (50 mL) was added and the reaction mixture extracted with diethyl ether (2 x 40 mL). The combined organic phases were washed with water (4 x 40 mL) and brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 30% ethyl acetate in hexanes→100% ethyl acetate) to give firstly the *bis*-alkylated material (**322**) as a yellow oil (4.62 mmol, 2.02 g, 77%, 1:1 mixture of diasteroisomers) and then the *mono*-alkylated material (**333**) (0.54 mmol, 94 mg, 9%) as a clear oil.

Data for **322**

Novel

IR (ATR / golden gate): 3054 (w), 2949 (w), 1730 (s), 1440 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.61–7.49 (10H, m, 10 x aromatic C**H**), 3.70–3.63 (6H, m, 2 x OC**H**$_3$), 2.84 (2H, m, $CH_2C\mathbf{H}_2SOPh$), 2.62 (2H, m, $CH_2C\mathbf{H}_2SOPh$), 2.36–2.22 (2H, m, $C\mathbf{H}_2CH_2SOPh$), 2.05 (2H, m, $C\mathbf{H}_2CH_2SOPh$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 170.5 (2x**C**=O), 143.2+143.2 (2x**C**), 131.3 (2x**C**H), 129.5 (4x**C**H), 124.2 (4x**C**H), 56.1+56.0 (**C**), 53.1 (2xO**C**H$_3$), 51.3+51.2 (2x**C**H$_2$), 25.6+25.5 (2x**C**H$_2$).

ESMS: *m/z* (%): 459 $[M+Na]^+$ (90), 895 $[M_2+Na]^+$ (100).

HRMS (ES +ve): $C_{21}H_{24}NaO_6S_2$ $[M+Na]^+$ 459.0906, found 459.0907.

Data for **333** consistent with the literature.[76]

IR (ATR / golden gate): 3054 (w), 3005 (w), 2949 (w), 1733 (s), 1422 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.65–7.45 (5H, m, 5 x aromatic C**H**), 3.72 (3H, s, OC**H**$_3$), 3.71 (3H, s, OC**H**$_3$), 3.52 (1H, t, *J*=7.2 Hz, C**H**CH$_2$CH$_2$SOPh), 2.94 (1H, m, C**H**H**S**OPh), 2.81 (1H, m, CH**H**SOPh), 2.35 (1H, m, C**H**HCH$_2$SOPh), 2.19 (1H, m, CH**H**CH$_2$SOPh).

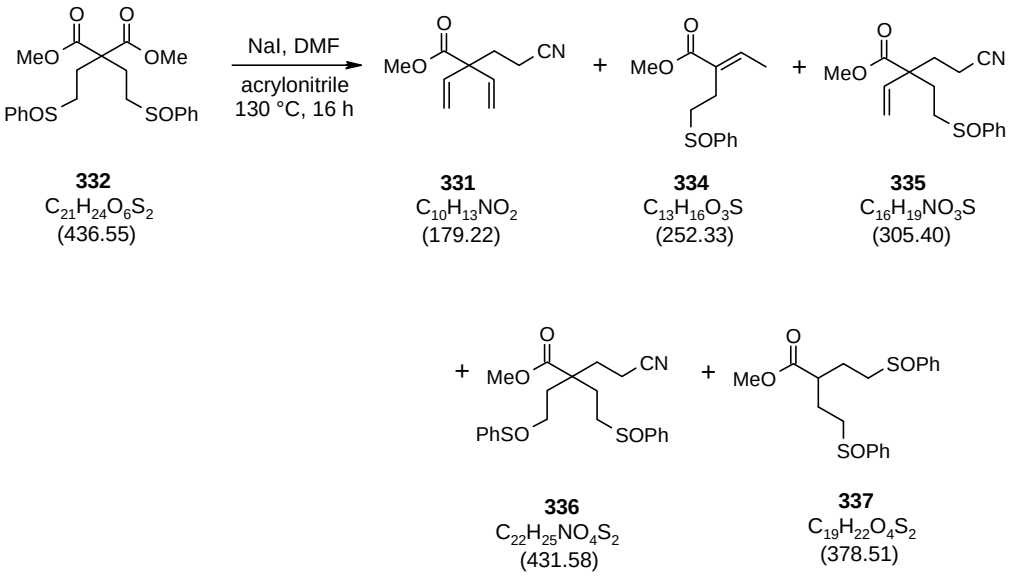
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 169.0+168.9 (2x**C**=O), 143.3+143.2 (**C**), 131.3 (**C**H), 129.5 (2x**C**H), 124.2 (2x**C**H), 53.9 (**C**H$_2$), 52.9 (2xO**C**H$_3$), 50.3 (**C**H), 21.6 (**C**H$_2$).

ESMS: *m/z* (%): 307 $[M+Na]^+$ (100).

HRMS (ES +ve): $C_{13}H_{16}NaO_5S$ $[M+Na]^+$ 307.0616, found 307.0611.

Methyl 4-cyano-2,2-divinyl-butanoate (331), methyl 2-(2-benzenesulfinyl-ethyl)-but-2-enoate (334), methyl 2-2(2-benzenesulfinyl-ethyl)-4-cyano-2-vinyl-butanoate (335), methyl 2,2,-*bis*-(2-benzenesulfinyl-ethyl)-4-cyano-butanoate (336) and methyl 4-benzenesulfinyl-2-(2-benzenesulfinyl-ethyl)-butanoate (337).



332
$C_{21}H_{24}O_6S_2$
(436.55)

331
$C_{10}H_{13}NO_2$
(179.22)

334
$C_{13}H_{16}O_3S$
(252.33)

335
$C_{16}H_{19}NO_3S$
(305.40)

336
$C_{22}H_{25}NO_4S_2$
(431.58)

337
$C_{19}H_{22}O_4S_2$
(378.51)

To a solution of malonate (**332**) (0.52 mmol, 0.23 g) in anhydrous DMF (5 mL) at room temperature under argon was added NaI (1.04 mmol, 42 mg) and acrylonitrile (2.60 mmol, 0.17 mL). The reaction mixture was heated to 130 °C for 16 h then cooled to room temperature and water (10 mL) added. After extraction with ethyl acetate (2 x 10 mL), the combined organic phases were washed with water (4 x 10 mL) and brine (30 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 20→50% ethyl acetate in hexanes to 1% MeOH in ethyl acetate) to give a mixture of compounds (**331**, **334**, **335**, **336** and **337**). Yields of each product varied with reaction conditions (temperature and time).

Data for **331**

Novel — Clear oil.

IR (ATR / golden gate): 3085 (w), 3009 (w), 2952 (w), 2250 (w), 1728 (s), 1433 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 5.97 (2H, dd, *J*=17.6, 10.8 Hz, 2 x C**H**=CH_2), 5.35 (2H, d, *J*=10.8 Hz, 2 x CH=C**H**H), 5.18 (2H, d,

J=17.6 Hz, 2 x CH=C**H**H), 3.75 (3H, s, OC**H**$_3$), 2.39 (2H, t, *J*=8.1 Hz, CH$_2$C**H**$_2$CN), 2.23 (2H, t, *J*=8.1 Hz, C**H**$_2$CH$_2$CN).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 173.0 (**C**=O), 137.0 (2x**C**H), 119.7 (**C**N), 117.4 (2x**C**H$_2$), 54.8 (**C**), 52.8 (O**C**H$_3$), 31.5 (**C**H$_2$), 13.2 (**C**H$_2$).

ESMS: *m/z* (%): 202 $[M+Na]^+$ (100).

HRMS (ES +ve): $C_{10}H_{13}NNaO_2$ $[M+Na]^+$ 202.0844, found 202.0838.

Data for **334**

Novel — Clear oil.

IR (ATR / golden gate): 3058 (w), 2990 (w), 2952 (w), 2850 (w), 1706 (s), 1644 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.65–7.60 (2H, m, 2 x aromatic C**H**), 7.56–7.49 (3H, m, 3 x aromatic C**H**), 6.97 (1H, q, *J*=7.2 Hz, C=C**H**CH$_3$), 3.71 (3H, s, OC**H**$_3$), 3.00 (1H, m, CH$_2$CH**H**SOPh), 2.88–2.76 (2H, m, C**H**HC**H**HSOPh), 2.59 (1H, m, CH**H**CH$_2$SOPh), 1.82 (3H, d, *J*=7.2 Hz, C=CHC**H**$_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 167.6 (**C**=O), 143.9 (**C**), 140.5 (**C**H), 131.1 (**C**H), 130.0 (**C**), 129.4 (2x**C**H), 124.2 (2x**C**H), 55.8 (**C**H$_2$), 52.0 (O**C**H$_3$), 19.6 (**C**H$_2$), 14.5 (**C**H$_3$).

ESMS: *m/z* (%): 253 $[M+H]^+$ (20), 275 $[M+Na]^+$ (80), 527 $[M_2+Na]^+$ (100).

HRMS (ES +ve): $C_{13}H_{16}NaO_3S$ $[M+Na]^+$ 275.0718, found 275.0712.

Data for **335**

Novel — Brown oil, 1:1 mixture of diastereoisomers.

IR (ATR / golden gate): 3047 (w), 2956 (w), 2245 (w), 1726 (s), 1443 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.63–7.48 (5H+5H, m, 2 x (5 x aromatic C**H**)), 5.876 (1H, dd, *J*=17.9, 11.0 Hz, C**H**=CH_2), 5.872 (1H, dd, *J*=17.9, 11.0 Hz, C**H**=CH_2), 5.35 (1H, d, *J*=11.0 Hz, CH=C**H**H), 5.29 (1H, d, *J*=11.0 Hz, CH=C**H**H), 5.15 (1H, d, *J*=17.9 Hz, CH=CH**H**), 5.06 (1H, d, *J*=17.9 Hz, CH=CH**H**), 3.71 (3H, s, OC$\mathbf{H}_3$), 3.69 (3H, s, OC$\mathbf{H}_3$), 2.85 (1H+1H, m, 2 x CH**H**), 2.64 (1H+1H, m, 2 x CH**H**), 2.32–2.06 (4H+4H, m, 2 x 4 x C**H**H), 2.04–1.85 (2H+2H, m, 2 x 2 CH**H**).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 173.4 (**C**=O), 143.4+143.3 (**C**), 136.7+136.7 (**C**H), 131.3 (**C**H), 129.5 (2x**C**H), 124.2 (2x**C**H), 119.2 (**C**N), 117.9+117.8 ($\mathbf{C}H_2$), 52.8+52.7 (O$\mathbf{C}H_3$), 51.7+51.5 ($\mathbf{C}H_2$), 51.1 (**C**), 32.5+32.3 ($\mathbf{C}H_2$), 28.1+27.8 ($\mathbf{C}H_2$), 13.0+12.9 ($\mathbf{C}H_2$).

ESMS: *m/z* (%): 328 $[M+Na]^+$ (100), 633 $[M_2+Na]^+$ (60).

HRMS (ES +ve): $C_{16}H_{19}NNaO_3S$ $[M+Na]^+$ 328.0977, found 328.0978.

Data for **336**

Novel Brown oil (1:2:1 mixture of diastereoisomers).

IR (ATR / golden gate): 3058 (w), 2945 (w), 2249 (w), 1725 (m), 1443 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.61–7.48 (10H, m, 10 x aromatic C**H**), 3.66–3.58 (3H, m, OC$\mathbf{H}_3$), 2.77–2.72 (2H, m, $CH_2C\mathbf{H}_2$SOPh), 2.58–2.43 (2H, m, $CH_2C\mathbf{H}_2$SOPh), 2.26–1.92 (4H, m, 4 x C**H**H), 1.91–1.83 (2H, m, 2 x CH**H**), 1.67–1.77 (2H, m, 2 x CH**H**).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 173.9 (**C**=O), 143.0+143.0+142.9+142.8 (2x**C**), 131.4 (2x**C**H), 129.5 (4x**C**H), 124.1 (4x**C**H), 118.8 (**C**N), 52.7 (O$\mathbf{C}H_3$), 50.7+50.6+50.5+50.3 (2x$\mathbf{C}H_2$),

47.3+47.2 (**C**), 30.8+30.7+30.6 (**C**H_2), 25.8+25.5+25.3 (2x**C**H_2), 12.4 (**C**H_2).

ESMS: *m/z* (%): 454 $[M+Na]^+$ (100), 885 $[M_2+Na]^+$ (100).

HRMS (ES +ve): $C_{22}H_{25}NNaO_4S_2$ $[M+Na]^+$ 454.1123, found 454.1117.

Data for **337**

Novel Brown oil (1:1 mixture of diastereoisomers).

IR (ATR / golden gate): 3054 (w), 2952 (w), 2930 (w), 2847 (w), 1726 (s), 1443 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.62–7.46 (10H, m, 10 x aromatic C**H**), 3.64 (3H, s, OC**H**$_3$), 2.88–2.42 (4H, m, 4 x C**H**H), 2.25–1.64 (5H, m, C**H**CH_2CH_2SOPh and 4 x CH**H**).

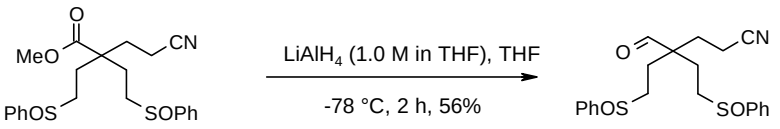
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 174.2+173.8 (**C**=O), 143.5+143.3 (2x**C**), 131.4 +131.3+131.2 (2x**C**H), 129.5+129.5+124.2 (4x**C**H), 124.1 (4x**C**H), 54.2+54.1+54.0+53.9 (2x**C**H_2), 52.2 (O**C**H_3), 43.5+43.3+43.2 (**C**H), 24.3+24.3+24.1+23.9 (2x**C**H_2).

ESMS: *m/z* (%): 401 $[M+Na]^+$ (50), 779 $[M_2+Na]^+$ (100).

HRMS (ES +ve): $C_{19}H_{22}NaO_4S_2$ $[M+Na]^+$ 401.0857, found 401.0822.

6-Benzenesulfinyl-4-(2-benzenesulfinyl-ethyl)-4-formyl-hexanenitrile (340).



336
$C_{22}H_{25}NO_4S_2$
(431.58)

340
$C_{21}H_{23}NO_3S_2$
(401.55)

To anhydrous THF (15 mL) under argon at −78 °C was added sequentially $LiAlH_4$ (1.0 M, 0.46 mmol, 0.46 mL) and a solution of nitrile (**336**) (0.23 mmol, 0.10 g), in anhydrous THF (5 mL) drop-wise. After 2 h the reaction was quenched by the drop-wise addition of water (30 mL) and the solution was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 100% ethyl acetate→5% MeOH in ethyl acetate) to give the aldehyde (**441**) (0.13 mmol, 52 mg, 56%) as a colourless oil.

Novel 1:2:1 mixture of diastereoisomers.

IR (ATR / golden gate): 3062 (w), 2952 (w), 2865 (w), 2249 (w), 1715 (m), 1443(m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

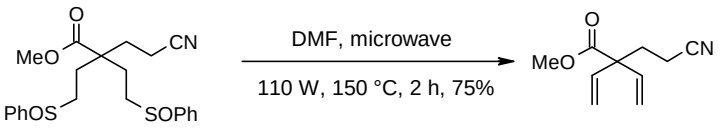
δ ppm 9.30 (1H, m, C**H**O), 7.59–7.46 (10H, m, 10 x aromatic C**H**), 2.80–2.63 (2H, m, 2 x C**H**H), 2.39–2.54 (2H, m, 2 x CH**H**), 2.21–1.92 (4H, m, 4 x C**H**H), 1.88–1.77 (2H, m, 2 x CH**H**), 1.72–1.59 (2H, m, 2 x CH**H**).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 202.3 (**C**HO), 142.7+142.6+142.6 (2x**C**), 131.5 (2x**C**H), 129.6 (4x**C**H), 124.0 (4x**C**H), 118.7 (**C**N), 50.4+50.4 (**C**), 49.8+49.7+49.6+49.5 (2x**C**H_2), 27.7 (**C**H_2), 23.0+22.8+22.7 (2x**C**H_2), 11.9 (**C**H_2).

ESMS: *m/z* (%): 456 $[M+Na+MeOH]^+$ (100).

Methyl 4-cyano-2,2-divinyl-butanoate (331).



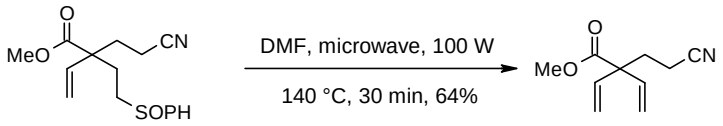
332
$C_{22}H_{25}NO_4S_2$
(431.58)

331
$C_{10}H_{13}NO_2$
(179.22)

A solution of nitrile (**332**) (0.63 mmol, 0.27 g) in anhydrous DMF (12 mL) was degassed with argon for 30 min. The solution was separated into 3 mL batches and heated under microwave irradiation (100 W, 150 °C) for 2–3 h. The dark brown solutions were combined and partitioned between water (20 mL) and ethyl acetate (20 mL). The aqueous phase was extracted with ethyl acetate (20 mL), and the combined organic phases were washed with water (4 x 20 mL) and brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 100% petroleum ether→25% diethyl ether in petroleum ether) to give divinyl ester (**331**) (0.47 mmol, 84 mg, 75%) as a yellow oil.

Data previously reported **331**.

Methyl 4-cyano-2,2-divinyl-butanoate (331).



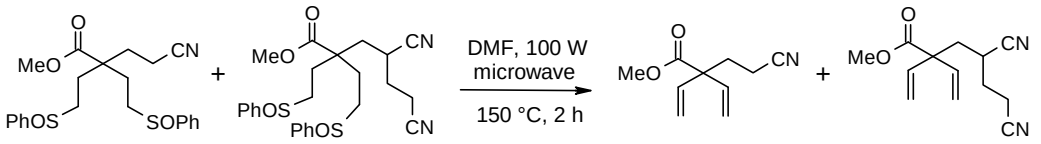
335
$C_{16}H_{19}NO_3S$
(305.40)

331
$C_{10}H_{13}NO_2$
(179.22)

A solution of nitrile (**335**) (0.53 mmol, 0.15 g) in anhydrous DMF (6 mL) was degassed with argon for 30 min. The solution was separated into 3 mL batches and heated under microwave irradiation (100 W, 140 °C) for 30 min. The dark brown solutions were combined and partitioned between water (10 mL) and ethyl acetate (10 mL). The aqueous phase was extracted with ethyl acetate (1 x 10 mL) and the combined organic phases combined were washed with water (4 x 20 mL) and brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 100% petroleum ether→25% diethyl ether in petroleum ether) to give the divinyl ester (**331**) (0.34 mmol, 61 mg, 64%) as a yellow oil.

Data previously reported **331**.

Methyl 4-cyano-2,2-divinyl-butanoate (331) and methyl 4,6-dicyano-2,2-divinyl-hexanoate (435).



336
$C_{22}H_{25}NO_4S_2$
(431.58)

434
$C_{25}H_{28}N_2O_4S_2$
(484.64)

331
$C_{10}H_{13}NO_2$
(179.22)

435
$C_{13}H_{16}N_2O_2$
(232.28)

A crude mixture (2:1) of nitrile (**336**) and nitrile (**434**) (100 mg) was dissolved in anhydrous DMF (3 mL) and heated under microwave irradiation (100 W, 130 °C) for 1 h. The resulting dark brown solution was partitioned between water (10 mL) and ethyl acetate (10 mL). The aqueous phase was extracted with ethyl acetate (10 mL), and the combined organic phases were washed with water (4 x 10 mL) and brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 100% petroleum ether→50% diethyl ether in petroleum ether) to give firstly the divinyl ester (**331**) (0.06 mmol, 10 mg) as a yellow oil and then the *bis*-nitrile compound (**435**) as a brown oil (0.13 mmol, 3 mg, 1:1 mixture of diastereoisomers).

Data previously reported for **331**.

Data for **435**

Novel

IR (ATR / golden gate): 3088 (w), 2952 (w), 2922 (w), 2847 (w), 2238 (w), 1726 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 6.08 (2H, dd, *J*=17.6, 10.7 Hz, 2 x C**H**=CH_2), 6.00 (2H, dd, *J*=17.6, 10.7 Hz, 2x C**H**=CH_2), 5.38 (2H+2H, dd, *J*=10.7, 3.5 Hz, 2 x CH=C**H**H), 5.22 (2H+2H, dd, *J*=17.6, 3.5 Hz, 2 x CH=CH**H**), 3.77 (3H+3H, s, OC**H**$_3$), 2.82 (1H+1H, m, C**H**HCHCN), 2.68–2.48 (2H+2H, m, $CHCH_2C$**H**$_2$CN), 2.35 (1H+1H,

dd, *J*=14.1, 9.4 Hz, C**H**HCH$_2$CN), 1.97–2.05 (3H+3H, m, C**H**C**H**$_2$CH$_2$CN).

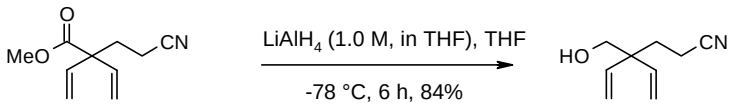
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 173.1 (**C**=O), 137.1+137.0 (2x**C**H), 126.6 (**C**N), 120.6 (**C**N), 118.0+117.9 (2x**C**H$_2$), 54.9 (**C**), 52.9 (O**C**H$_3$), 38.5 (**C**H$_2$), 29.9 (**C**H$_2$), 27.2 (**C**H), 15.4 (**C**H$_2$).

ESMS: *m/z* (%): 255 $[M+Na]^+$ (100).

HRMS (ES +ve): $C_{13}H_{16}N_2NaO_2$ $[M+Na]^+$ 255.1109, found 255.1104.

4-Hydroxymethyl-4-vinyl-hex-5-enenitrile (341).



331
$C_{10}H_{13}NO_2$
(179.22)

341
$C_9H_{13}NO$
(151.21)

To a solution of ester (**331**) (1.42 mmol, 0.25 g) in anhydrous THF (20 mL), under argon at −78 °C, was added $LiAlH_4$ (1.0 M in THF, 2.84 mmol, 2.8 mL) drop-wise. After 6 h water (5 mL) was added, the reaction mixture was warmed to room temperature and partitioned between HCl (2 M, 10 mL) and ether (20 mL). The aqueous phase was extracted with ether (2 x 20 mL) and the combined organic phases were washed with brine (60 mL), dried ($MgSO_4$), concentrated *in vacuo* to give alcohol (**341**) (1.19 mmol, 0.18 g, 84%) as a yellow oil.

Novel

IR (ATR / golden gate): 3444 (m), 3092 (w), 2930 (w), 2869 (w), 2245 (m), 1716 (w), 1629 (w).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

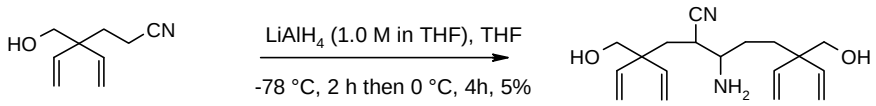
δ ppm 5.74 (2H, dd, *J*=17.7, 10.9 Hz, 2 x C**H**=CH_2), 5.33 (2H, dd, *J*=10.9, 0.6 Hz, 2 x CH=C**H**H), 5.15 (2H, dd, *J*=17.7, 0.6 Hz, 2 x CH=CH**H**), 3.53 (2H, s, C**H**$_2$OH), 2.32 (2H, t, *J*=8.2 Hz, CH_2C**H**$_2$CN), 1.97 (2H, t, *J*=8.2 Hz, C**H**$_2$$CH_2$CN), 1.65 (1H, b s, CH_2O**H**).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 139.2 (2x**C**H), 120.3 (2x**C**H_2), 117.4 (**C**N), 67.1 (O**C**H_2), 48.5 (**C**), 30.1 (**C**H_2), 12.6 (**C**H_2).

CIMS: *m/z* (%): 169 $[M+NH_4]^{+\cdot}$ (50), 152 $[M+H]^{+\cdot}$ (10), 134 $[M\text{-}OH]^{+\cdot}$ (50), 121 $[M-CH_2OH]^{+\cdot}$ (70).

3-Amino-6-hydroxymethyl-2-(2-hydroxymethyl-2-vinyl-but-3-enyl)-6-vinyl-oct-7-enenitrile (342).



331
$C_9H_{13}NO$
(151.21)

342
$C_{18}H_{28}N_2O_2$
(304.44)

To a solution of ester (**331**) (0.67 mmol, 0.12 g) in anhydrous THF (10 mL), under argon at −78°C, was added $LiAlH_4$ (1.0 M in THF, 2.68 mmol, 2.7 mL) drop-wise. After 2 h the reaction mixture was allowed to warm to 0 °C. After 4 h water (20 mL) was added, and the reaction mixture warmed to room temperature and extracted with ether (3 x 20 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 5% MeOH in ethyl acetate) to give firstly RSM (**331**) (0.05 mmol, 8 mg, 7%) and then (**342**) (0.03 mmol, 10 mg, 5%, 1:1 mixture of stereoisomers) as a yellow oil.

Novel

IR (ATR / golden gate): 3357 (w), 3077 (w), 3002 (w), 2922 (w), 2858 (w), 2234 (w), 1625 (w).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

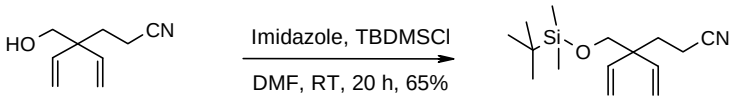
δ ppm 5.89 - 5.70 (4H, m, 4 x C**H**=CH_2), 5.36–5.06 (8H, m, 4 x CH=C**H**$_2$), 3.63 (2H, s, C**H**$_2$OH), 3.58–3.54 (2H, m, C**H**$_2$OH), 2.81 (1H, m, C**H**CN or C**H**NH_2), 2.62 (1H, m, C**H**CN or C**H**NH_2), 2.11–1.61 (6H, m, 2 x C**H**$_2$, and 2 x O**H**), 1.60–1.22 (2H, m, C**H**$_2$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 141.1+141.0+140.9+140.8 (2x(2x**C**H)), 140.2+140.0+139.9+139.8 (2x(2x**C**H)), 122.1+121.4 (2x**C**N), 117.0+116.9+116.9+116.8 (2x(2x**C**H_2)), 116.2+116.1+116.1 (2x(2x**C**H_2)), 66.9+66.8+66.7

	+66.2 (2x(2x**C**CH_2)), 55.1 (2x**C**H), 48.7+48.6 (2x**C**), 48.5 (2x**C**), 35.4+34.8 (2x**C**H), 34.4 (2x**C**H_2), 31.5+31.3 (2x**C**H_2), 30.4+28.6 (2x**C**H_2).
ESMS: *m/z* (%):	327 $[M+Na]^+$ (100), 305 $[M+H]^+$ (60).
HRMS (ES +ve):	$C_{18}H_{29}N_2O_2$ $[M+H]^+$ 305.2229, found 305.2222.

4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-vinyl-hex-5-enenitrile (343).



341
$C_9H_{13}NO$
(151.21)

343
$C_{15}H_{27}NOSi$
(265.47)

To a solution of alcohol (**341**) (1.19 mmol, 0.18 g) and imidazole (2.38 mmol, 0.15 g) in anhydrous DMF (5 mL) at room temperature under argon was added a solution of TBDMSCl (1.43 mmol, 0.22 g) in anhydrous DMF (1 mL). After 16 h further imidazole (2.38 mmol, 0.15 g) and TBDMSCl (1.43 mmol, 0.22 g) were added, followed after 4 h by HCl (2 M, 10 mL). The reaction mixture was extracted with ether (3 x 10 mL) and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 5% diethyl ether in petroleum ether) to give the silyl ether (**343**) (0.77 mmol, 0.21 g, 65%) as a colourless oil.

Novel

IR (ATR / golden gate): 3081 (w), 3952 (w), 2933 (w), 2892 (w), 2854 (w), 1470 (w), 1459 (w).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 5.76 (2H, dd, *J*=17.8, 11.0 Hz, 2 x C**H**=CH_2), 5.23 (2H, dd, *J*=11.0, 1.0 Hz, 2 x CH=C**H**H), 5.06 (2H, dd, *J*=17.8, 1.0 Hz, 2 x CH=CH**H**), 3.49 (2H, s, C**H**$_2$OSi$(CH_3)_2$C$(CH_3)_3$), 2.34–2.25 (2H, m, CH_2C**H**$_2$CN), 1.93–2.03 (2H, m, C**H**$_2$$CH_2$CN), 0.90 (9H, s, OSi$(CH_3)_2$C(C**H**$_3$)$_3$), 0.04 (6H, s, OSi(C**H**$_3$)$_2$C$(CH_3)_3$).

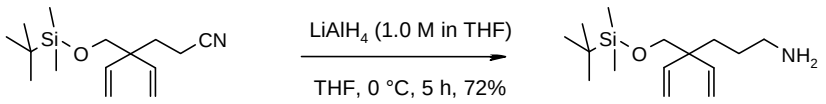
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 139.8 (2x**C**H), 120.6 (**C**N), 116.2 (2x**C**H_2), 68.3 (**C**H_2), 48.0 (**C**), 30.3 (**C**H_2), 26.0 (3x**C**H_3), 18.4 (**C**), 12.7 (**C**H_2), −5.4 (2x**C**H_3).

ESMS: *m/z* (%): 288 $[M+Na]^+$ (100).

HRMS (ES +ve): $C_{15}H_{27}NNaOSi$ $[M+Na]^+$ 288.1759, found 288.1754.

4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-vinyl-hex-5-enylamine (344).



343
$C_{15}H_{27}NOSi$
(265.47)

344
$C_{15}H_{31}NOSi$
(269.51)

To a solution of nitrile (**343**) (0.61 mmol, 0.16 g) in anhydrous THF (20 mL) at 0 °C under argon was added a solution of $LiAlH_4$ (1.0 M in THF, 1.20 mmol, 1.2 mL) drop-wise. After 5 h water (10 mL) was added and the reaction mixture extracted with ether (3 x 10 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 100% ethyl acetate then 1:9:90, NH_4OH: MeOH: ethyl acetate) to give amine (**344**) as a colourless oil (0.44 mmol, 0.12 g, 72%).

Novel

IR (ATR / golden gate): 3081 (w), 2949 (m), 2930 (m), 2888 (m), 2850 (m), 1637 (w), 1565 (w).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 5.80 (2H, dd, *J*=17.8, 10.9 Hz, 2 x C**H**=CH_2), 5.11 (2H, dd, *J*=10.9, 1.4 Hz, 2 x CH=C**H**H), 5.01 (2H, dd, *J*=17.8, 1.4 Hz, 2 x CH=CH**H**), 3.51 (2H, s, OC**H**$_2$), 2.67 (2H, t, *J*=7.0 Hz, C**H**$_2$$NH_2$), 1.60 (2H, b s, CH_2N**H**$_2$), 1.56–1.49 (2H, m, C**H**HC**H**HCH_2NH_2), 1.45–1.35 (2H, m, CH**H**CH**H**CH_2NH_2), 0.88 (9H, s, (C**H**$_3$)$_3$), 0.02 (6H, s, Si(C**H**$_3$)$_2$).

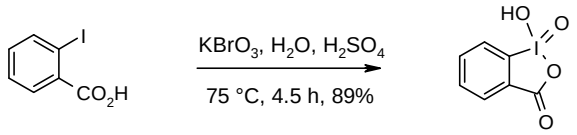
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 142.2 (2x**C**H), 114.4 (2x**C**H_2), 68.2 (**C**H_2), 48.1 (**C**H_2), 43.0 (**C**H_2), 32.0 (**C**H_2), 28.2 (**C**), 26.1 (3x**C**H_3), 18.5 (**C**), −5.3 (2x**C**H_3).

CIMS: *m/z* (%): 270 $[M+H]^{+\cdot}$ (100), 212 $[(M-{}^tBu)+H]^{+\cdot}$ (70), 138 (20), 89 (20), 73 (50).

HRMS (ES +ve): $C_{15}H_{32}NOSi$ $[M+H]^+$ 270.2253, found 270.2248.

***o*-Iodoxybenzoic acid (IBX) (437).**



436
$C_7H_5IO_2$
(248.02)

437
$C_7H_5IO_4$
(280.02)

To a suspension of 2-iodobenzoic acid (**436**) (40.3 mmol, 10.00g) in H_2SO_4 (0.73 M, 100 mL) was added potassium bromate (52.4 mmol, 8.75 g). The reaction mixture was heated to 75 °C for 4.5 h with reaction gasses scrubbed through a saturated solution of sodium thiosulfate. The reaction mixture was cooled to room temperature and stirred for 16 h. The resulting precipitate was collected by filtration, washing with water (200 mL) and ethanol (100 mL). The white solid product (**437**) was dried under vacuum to give the desired product (35.7 mmol, 9.99 g, 89%). Data consistent with the literature.[77]

IR (ATR / golden gate): 2896 (m), 1633 (s), 1564 (s).

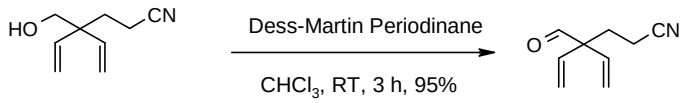
^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 8.15 (1H, d, *J*=7.9 Hz, aromatic C**H**), 8.07–7.96 (2H, m, 2 x aromatic C**H**), 7.84 (1H, app. t, *J*=7.2 Hz, aromatic C**H**).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 167.5 (**C**=O), 146.6 (**C**), 133.4 (**C**H), 133.0 (**C**H), 131.4 (**C**), 130.1 (**C**H), 125.0 (**C**H).

4-Formyl-4-vinyl-hex-5-enenitrile (347).



341
$C_9H_{13}NO$
(151.21)

347
$C_9H_{11}NO$
(149.19)

To a solution of Dess-Martin periodinane (0.18 mmol, 77 mg) in $CHCl_3$ (2 mL), at room temperature was added a solution of alcohol **341** (0.17 mmol, 25 mg) in $CHCl_3$ (0.5 mL). After 3 h the reaction mixture was concentrated *in vacuo* with silica (2 g) and purified by column chromatography (dry loaded, silica, 30% diethyl ether in petroleum ether) to give the aldehyde (**347**) as a yellow oil (0.16 mmol, 24 mg, 95%).

Novel

IR (ATR / golden gate): 3085 (w), 3020 (w), 2941 (w), 2824 (w), 2722 (w), 2245 (w), 1722 (s), 1633 (w).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

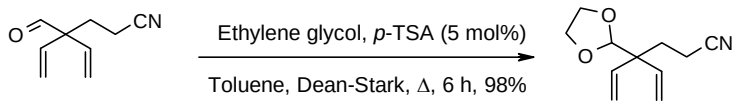
δ ppm 9.31 (1H, s, C**H**O), 5.77 (2H, dd, *J*=17.8, 10.8 Hz, 2 x C**H**=CH_2), 5.51 (2H, d, *J*=10.8 Hz, 2 x CH=C**H**H), 5.23 (2H, d, *J*=17.8 Hz, 2 x CH=CH**H**), 2.39–2.27 (2H, m, $CH_2C\mathbf{H}_2CN$), 2.16–2.06 (2H, m, $C\mathbf{H}_2CH_2CN$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 197.7 (**C**HO), 135.0 (2x**C**H), 120.7 (2x**C**H_2), 119.7 (**C**N), 59.3 (**C**), 29.6 (**C**H_2), 12.8 (**C**H_2).

ESMS: *m/z* (%): 172 $[M+Na]^+$ (100).

4-[1,3]Dioxolan-2-yl-4-vinyl-hex-5-enenitrile (348).



347
$C_9H_{11}NO$
(149.19)

348
$C_{11}H_{15}NO_2$
(193.25)

To a solution of aldehyde (**347**) (0.47 mmol, 70 mg) in toluene (2 mL) was added ethylene glycol (2.35 mmol, 0.13 mL) and *p*-TSA (0.03 mmol, 6 mg). The reaction mixture was heated to reflux under a Dean-Stark trap for 6 h then cooled to room temperature, diluted with ether (10 mL) and washed with sat. K_2CO_3 (20 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give acetal **348** as a yellow oil (0.46 mmol, 89 mg, 98%).

Novel

IR (ATR / golden gate): 3088 (w), 2983 (w), 2949 (w), 2888 (m), 2245 (m), 1735 (w), 1633 (w).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 5.84 (2H, dd, *J*=17.8, 11.0 Hz, 2 x C**H**=CH_2), 5.35 (2H, dd, *J*=11.0, 0.6 Hz, 2 x CH=C**H**H), 5.18 (2H, dd, *J*=17.8, 0.6 Hz, 2 x CH=CH**H**), 4.73 (1H, s, C**H**CH_2CH_2O), 4.02–3.81 (4H, m, O**C**H_2**C**H_2O), 2.39–2.29 (2H, m, CH_2**C**H_2CN), 2.09–2.00 (2H, m, **C**H_2CH_2CN).

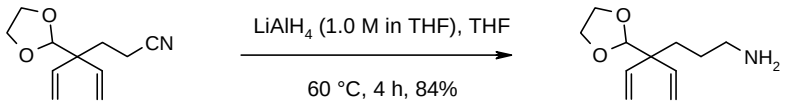
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 137.4 (2x**C**H), 120.5 (**C**N), 117.9 (2x**C**H_2), 107.6 (**C**H), 65.4 (2x**C**H_2), 50.4 (**C**), 28.4 (**C**H_2), 12.7 (**C**H_2).

ESMS: *m/z* (%): 216 $[M+Na]^+$ (100).

HRMS (ES +ve): $C_{11}H_{15}NNaO_2$ $[M+Na]^+$ 216.1000, found 216.0995.

4-[1,3]Dioxolan-2-yl-4-vinyl-hex-5-enylamine (349).



348
$C_{11}H_{15}NO_2$
(193.25)

349
$C_{11}H_{19}NO_2$
(197.28)

To a solution of nitrile (**348**) (1.76 mmol, 0.34 g) in anhydrous THF (15 mL) at 0 °C under argon was added a solution of $LiAlH_4$ (1.0 M in THF, 1.76 mmol, 1.76 mL) drop-wise. The reaction mixture was warmed to 60 °C then cooled to room temperature after 4 h. Water (15 mL) was added to the reaction mixture cautiously, followed by NaOH (2 M, 10 mL). The mixture was extracted with ether (5 x 20 mL), the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give amine (**349**) (1.48 mmol, 0.29 g, 84%) as yellow oil.

Novel

IR (ATR / golden gate): 3361 (w), 3088 (w), 2949 (m), 2873 (m), 1667 (w), 1637 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 5.89 (2H, dd, *J*=17.8, 11.0 Hz, 2 x C**H**=CH_2), 5.27 (2H, dd, *J*=11.0, 1.1 Hz, 2 x CH=C**H**H), 5.15 (2H, dd, *J*=17.8, 1.1 Hz, 2 x CH=CH**H**), 4.81 (1H, s, C**H**OCH_2CH_2O), 3.99–3.82 (4H, m, OC**H**$_2$C**H**$_2$O), 2.67 (2H, t, *J*=7.0 Hz, CH_2CH_2C**H**$_2$$NH_2$), 1.68–1.60 (2H, m, C**H**HC**H**HCH_2NH_2), 1.50–1.38 (2H, m, CH**H**CH**H**CH_2NH_2).

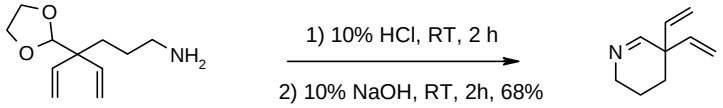
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 139.1 (2x**C**H), 116.5 (2x**C**H_2), 108.1 (**C**H), 65.5 (2x**C**H_2), 50.6 (**C**), 43.2 (**C**H_2), 30.7 (**C**H_2), 28.5 (**C**H_2).

ESMS: *m/z* (%): 198 $[M+H]^+$ (100).

HRMS (ES +ve): $C_{11}H_{20}NO_2$ $[M+H]^+$ 198.1494, found 198.1489.

5,5-Divinyl-2,3,4,5-tetrahydropyridine (233).



349
$C_{11}H_{19}NO_2$
(197.28)

233
$C_9H_{13}N$
(135.21)

To amine (**349**) (1.52 mmol, 0.30 g) was added 10% HCl (1.0 mL) and the mixture stirred at room temperature for 2 h. NaOH (10%) was added until the solution was pH 9 and after 2 h the reaction mixture was extracted with ether (4 x 10 mL). The combined organic phases were, dried ($MgSO_4$) and concentrated *in vacuo* to give imine (**233**) as a yellow oil (1.04 mmol, 140 mg, 68%).

Novel

IR (ATR / golden gate): 3776 (w), 3077 (w), 3005 (w), 2930 (m), 2865 (m), 1663 (m), 1633 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.53 (1H, b s, N=C**H**), 5.75 (2H, dd, *J*=17.6, 10.5 Hz, 2 x C**H**=CH_2), 5.21 (2H, d, *J*=10.5 Hz, 2 x CH=C**H**H), 5.08 (2H, d, *J*=17.6 Hz, 2 x CH=CH**H**), 3.60–3.54 (2H, m, NC**H**$_2$$CH_2CH_2$), 1.76–1.70 (2H, m, NCH_2C**H**HC**H**H), 1.66–1.59 (2H, m, NCH_2CH**H**CH**H**).

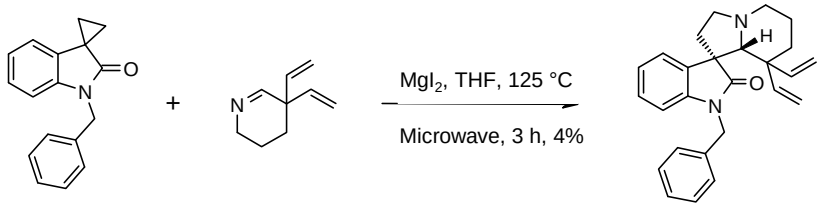
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 164.3 (**C**H), 141.5 (2x**C**H), 115.9 (2x**C**H_2), 49.6 (**C**H_2), 47.8 (**C**), 30.5 (**C**H_2), 18.5 (**C**H_2).

ESMS: *m/z* (%): 136 $[M+H]^+$ (90).

HRMS (ES +ve): Compound too unstable for HRMS.

1′-Benzyl-8,8-divinyl-octahydrospiro[indolizine1,3′-indol-2′-one] (350).



287
$C_{17}H_{15}NO$
(249.32)

233
$C_9H_{13}N$
(135.21)

350
$C_{26}H_{28}N_2O$
(384.53)

A solution of cyclopropane **287** (0.53 mmol, 0.13 g), imine **233** (0.48 mmol, 65 mg) and anhydrous MgI_2 (0.24 mmol, 67 mg) in anhydrous THF (2 mL) was heated to 125 °C under microwave irradiation for 3 h, cooled to room temperature, then partitioned between water (20 mL) and ethyl acetate (20 mL). The aqueous phase was extracted with ethyl acetate (4 x 20 mL), the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 20% diethyl ether in petroleum ether) to give firstly recovered staring material **287** (0.34 mmol, 84 mg, 64%) and then the desired product **350** as a colourless oil (0.002 mmol, 7 mg, 4%).

Novel

IR (ATR / golden gate): 3081 (w), 3054 (w), 3013 (w), 2933 (w), 2862 (w), 2805 (w), 1703 (s), 1607 (m), 1486 (m), 1463 (m).

^{1}H NMR (400 MHz, CHLOROFORM-*d*)

δ ppm 7.43 (1H, d, *J*=7.4 Hz, aromatic C**H**), 7.38–7.25 (5H, m, 5 x aromatic C**H**), 7.13 (1H, app. td, *J*=7.7, 1.1 Hz, aromatic C**H**), 6.93 (1H, app. td, *J*=7.6, 0.9 Hz, aromatic C**H**), 6.74 (1H, d, *J*=7.8 Hz, aromatic C**H**), 6.41 (1H, dd, *J*=17.8, 10.9 Hz, C**H**=CH_2), 5.21 (1H, dd, *J*=17.8, 10.9 Hz, C**H**=CH_2), 4.92 (1H, d, *J*=15.2 Hz, NC**H**HPh), 4.91 (1H, dd, *J*=17.8, 1.3 Hz, CH=C**H**H), 4.79 (1H, d, *J*=15.3 Hz, NCH**H**Ph), 4.77 (1H, dd, *J*=10.9, 1.3 Hz, CH=CH**H**), 4.60 (1H, dd, *J*=10.9, 1.3 Hz, CH=C**H**H), 4.43 (1H, dd, *J*=17.8, 1.3 Hz, CH=CH**H**), 3.42 (1H, app. td, *J*=8.8, 3.1 Hz,

$CCH_2C\mathbf{H}HN$), 3.33 (1H, dd, *J*=10.8, 4.0 Hz, $NC\mathbf{H}HCH_2CH_2C$), 2.59 (1H, s, NC**H**), 2.54 (1H, app. t, *J*=8.8 Hz, $CCH_2CH\mathbf{H}N$), 2.31 (1H, ddd, *J*=12.7, 8.8, 3.1 Hz, $CC\mathbf{H}HCH_2N$), 2.18 (1H, td, *J*=11.7, 3.1 Hz, $NCH\mathbf{H}CH_2CH_2C$), 1.99 (1H, dt, *J*=12.7, 8.8 Hz, $CCH\mathbf{H}CH_2N$), 1.83 (1H, ddd, *J*=12.7, 4.1, 4.0 Hz, $NCH_2C\mathbf{H}HCH_2C$), 1.66–1.52 (2H, m, $NCH_2CH\mathbf{H}CH_2C$ and $NCH_2CH_2C\mathbf{H}HC$), 1.45 (1H, m, $NCH_2CH_2CH\mathbf{H}C$).

^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*)

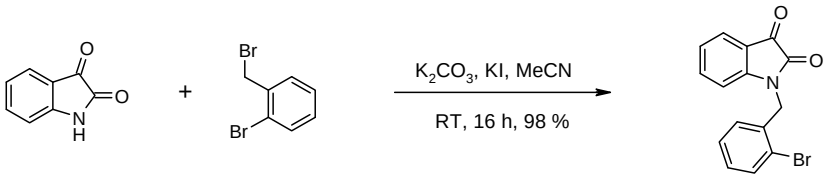
δ ppm 180.6 (**C**=O), 142.5 (**C**), 142.2 (**C**H), 141.5 (**C**H), 136.2 (**C**), 133.1 (**C**), 128.8 (2x**C**H), 128.1 (2x**C**H), 127.9 (**C**H), 127.8 (**C**H), 127.8 (**C**H), 121.5 (**C**H), 114.9 (**C**H_2), 112.6 (**C**H_2), 108.5 (**C**H), 80.0 (**C**H), 55.8 (**C**), 55.2 (**C**H_2), 54.6 (**C**H_2), 46.4 (**C**), 44.4 (**C**H_2), 38.3 (**C**H_2), 37.1 (**C**H_2), 21.8 (**C**H_2).

^{1}H-^{1}H and ^{1}H-^{13}C correlations obtained to confirm above NMR assignments.

ESMS: *m/z* (%): 385 $[M+H]^+$ (100), 407 $[M+Na]^+$ (10).

HRMS (ES +ve): $C_{26}H_{29}N_2O$ $[M+H]^+$ 385.2274, found 385.2275.

1-(2-Bromo-benzyl)-1*H*-indole-2,3-dione (351).



293
$C_8H_5NO_2$
(147.13)

438
$C_7H_6Br_2$
(249.93)

351
$C_{15}H_{10}BrNO_2$
(316.16)

To a solution of isatin (**293**) (13.59 mmol, 2.00 g) in acetonitrile (100 mL) at room temperature under argon, was added K_2CO_3 (27.19 mmol, 3.76 g) and KI (1.36 mmol, 0.23 g). After 30 min 2-bromobenzyl bromide (**438**) (13.59 mmol, 3.40 g) in acetonitrile (30 mL) was added. After a further 16 h the reaction mixture was partitioned between ethyl acetate (100 mL) and water (100 mL). The aqueous phase was separated and extracted with ethyl acetate (3 x 50 mL) and the combined organic phases were washed with brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **351** as an orange solid (13.27 mmol, 4.19 g, 98%).

Novel

Mpt: °C 180-182 °C (EtOH).

IR (ATR / golden gate): 3085 (w), 3054 (w), 3026 (w), 1732 (s), 1605 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.68–7.60 (2H, m, 2 x aromatic C**H**), 7.51 (1H, app. td, *J*=7.8, 1.3 Hz, aromatic C**H**), 7.31–7.09 (4H, m, 4 x aromatic C**H**), 6.75 (1H, d, *J*=7.8 Hz, aromatic C**H**), 5.06 (2H, s, NC**H**$_2$Ar).

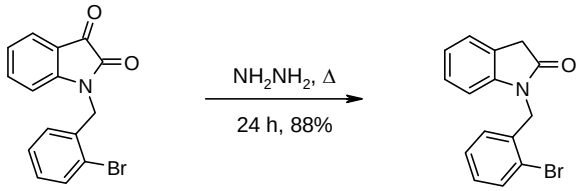
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 183.1 (**C**=O), 168.2 (**C**=O), 158.6 (**C**), 150.7 (**C**), 138.7 (**C**H), 133.4 (**C**H), 129.8 (**C**H), 128.2 (**C**H), 128.2 (**C**H), 125.7 (**C**H), 124.3 (**C**H), 123.0 (**C**), 117.9 (**C**), 111.3 (**C**H), 44.2 (**C**H$_2$).

ESMS: *m/z* (%): 338:340 {1:1} $[M+Na]^+$ Br^{79}:Br^{81} (100).

HRMS (ES +ve): $C_{15}H_{10}BrNNaO_2$ $[M+Na]^+$ 337.9793, found 337.9787.

1-(2-Bromo-benzyl)-1,3-dihydro-indol-2-one (352).



351
$C_{15}H_{10}BrNO_2$
(316.16)

352
$C_{15}H_{12}BrNO$
(302.17)

To hydrazine *mono*-hydrate (20 mL) was added **351** (13.25 mmol, 4.19 g). The reaction mixture was stirred under argon at 125 °C for 24 h, the cooled to room temperature, poured onto ice water (100 mL) and extracted with ethyl acetate (4 x 100 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **352** as a light brown solid (11.68 mmol, 3.53 g, 88%).

Novel

Mpt: °C 102-104 °C (EtOH).

IR (ATR / golden gate): 3062 (w), 3036 (w), 2949 (w), 2915 (w), 1703 (s), 1612 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.60 (1H, dd, *J*=7.7, 1.1 Hz, aromatic C**H**), 7.29 (1H, d, *J*=7.3 Hz, aromatic C**H**), 7.24–7.01 (5H, m, 5 x aromatic C**H**), 6.66 (1H, d, *J*=7.7 Hz, aromatic C**H**), 5.03 (2H, s, COC**H**$_2$), 3.69 (2H, s, NC**H**$_2$Ar).

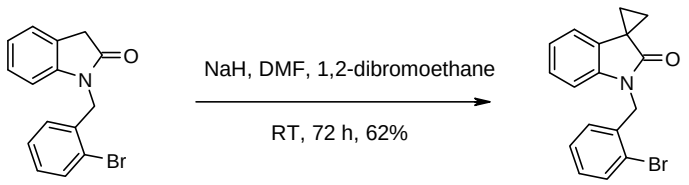
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 175.4 (**C**=O), 144.2 (**C**), 134.6 (**C**), 133.1 (**C**H), 129.2 (**C**H), 128.1 (**C**H), 127.9 (**C**H), 127.8 (**C**H), 124.6 (**C**H), 124.5 (**C**), 122.9 (**C**), 122.8 (**C**H), 109.3 (**C**H), 43.9 (**C**H$_2$), 36.0 (**C**H$_2$).

ESMS: *m/z* (%): 324:326 {1:1} $[M+Na]^+$ Br^{79}:Br^{81} (100).

HRMS (ES +ve): $C_{15}H_{12}BrNNaO$ $[M+Na]^+$ 323.9999, found 323.9994.

1′-(2-Bromo-benzyl)-spiro[cyclopropane-1,3′-indol-2′-one] (353).



352
$C_{15}H_{12}BrNO$
(302.17)

353
$C_{17}H_{14}BrNO$
(328.21)

To a solution of **352** (11.68 mmol, 3.53 g) in anhydrous DMF (50 mL) at 0 °C under argon, was added NaH (60% in mineral oil, 25.70 mmol, 1.03 g). After 1 h 1,2-dibromoethane (46.72 mmol, 4.0 mL) was added and the reaction mixture allowed to warm to room temperature and stirred for 72 h. Water (100 mL) and ethyl acetate (100 mL) were added and the aqueous separated and washed with ethyl acetate (100 mL). The combined organic phases were washed with water (4 x 100 mL), brine (200 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 10% ethyl acetate in hexanes) to give the cyclopropane **353** as a red solid (7.27 mmol, 2.39 g, 62%) and recovered starting material (0.35 mmol, 0.11 g, 3%).

Novel

Mpt: °C 115-117 °C (EtOH).

IR (ATR / golden gate): 3058 (w), 2990 (w), 2930 (w), 1708 (s), 1614 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

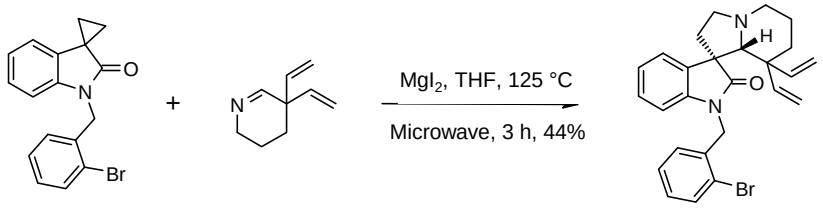
δ ppm 7.61 (1H, dd, *J*=7.8, 1.2 Hz, aromatic C**H**), 7.25–7.00 (5H, m, 5 x aromatic C**H**), 6.90 (1H, d, *J*=7.3 Hz, aromatic C**H**), 6.75 (1H, d, *J*=7.8 Hz, aromatic C**H**), 5.11 (2H, s, NC**H**$_2$Ar), 1.86 (2H, dd, *J*=7.8, 4.0 Hz, C**H**HC**H**H cyclopropane), 1.62 (2H, dd, *J*=7.8, 4.0 Hz, CH**H**CH**H** cyclopropane).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 177.4 (**C**=O), 142.5 (**C**), 135.0 (**C**), 133.0 (**C**H), 130.8 (**C**), 129.1 (**C**H), 127.9 (2x**C**H), 127.0 (**C**H),

	122.8 (**C**), 122.4 (**C**H), 118.5 (**C**H), 109.2 (**C**H), 44.3 (**C**H_2), 27.3 (**C**), 19.7 (2x**C**H_2).
ESMS: *m/z* (%):	350:352 {1:1} $[M+Na]^+$ Br^{79}:Br^{81} (100).
HRMS (ES +ve):	$C_{17}H_{14}BrNNaO$ $[M+Na]^+$ 350.0156 found 350.0151.

1′-(2-Bromo-benzyl)-8,8-divinyl-octahydrospiro[indolizine1,3′-indol-2′-one] (354).



353
$C_{17}H_{14}BrNO$
(328.21)

233
$C_9H_{13}N$
(135.21)

354
$C_{26}H_{27}BrN_2O$
(463.42)

To a solution of cyclopropane **353** (1.14 mmol, 0.37 g) in anhydrous THF (5 mL) was added imine **233** (1.04 mmol, 0.14 g) and anhydrous MgI_2 (1.14 mmol, 0.32 g). The reaction mixture was split into 2 portions and each was heated sequentially to 125 °C under microwave irradiation for 3 h then cooled to room temperature, combined and partitioned between water (40 mL) and ethyl acetate (40 mL). The aqueous phase was extracted with ethyl acetate (4 x 30 mL) and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 10→40% diethyl ether in petroleum ether) to give firstly recovered staring material **353** (0.39 mmol, 0.13 g, 34%) and then the desired product **354** as a colourless oil (0.46 mmol, 0.21 g, 44%).

Novel

IR (ATR / golden gate): 3085 (w), 3058 (w), 3009 (w), 2930 (w), 2865 (w), 2801 (w), 1705 (m), 1610 (m), 1486 (m), 1467 (m).

^{1}H NMR (400 MHz, CHLOROFORM-*d*)

δ ppm 7.60 (1H, dd, *J*=7.7, 1.1 Hz, aromatic C**H**), 7.46 (1H, dd, *J*=7.4, 0.7 Hz, aromatic C**H**), 7.20 (1H, app. td, *J*=7.4, 1.1 Hz, aromatic C**H**), 7.16–7.08 (3H, m, 3 x aromatic C**H**), 6.95 (1H, app. td, *J*=7.7, 0.7 Hz, aromatic C**H**), 6.64 (1H, d, *J*=7.8 Hz, aromatic C**H**), 6.43 (1H, dd, *J*=17.7, 10.9 Hz, C**H**=CH_2), 5.37 (1H, dd, *J*=17.7, 10.9 Hz, C**H**=CH_2), 5.05–4.91 (4H, m, CH=C**H**$_2$ and NC**H**$_2$Ar), 4.66 (1H, dd, *J*=10.9, 1.5 Hz, CH=C**H**H), 4.52 (1H, dd, *J*=17.9, 1.5 Hz, CH=CH**H**), 3.43 (1H, td, *J*=8.5, 3.1 Hz, CCH_2C**H**HN), 3.34 (1H,

dd, *J*=10.9, 3.8 Hz, NC**H**HCH$_2$CH$_2$C), 2.64 (1H, s, NC**H**), 2.58 (1H, app. q, *J*=9.0 Hz, CCH$_2$CH**H**N), 2.33 (1H, ddd, *J*=12.7, 9.0, 3.1 Hz, CC**H**HCH$_2$N), 2.20 (1H, td, *J*=11.7, 3.1 Hz. NCH**H**CH$_2$CH$_2$C), 2.03 (1H, dt, *J*=12.7, 8.5 Hz, CCH**H**CH$_2$N), 1.85 (1H, dt, *J*=12.6, 3.8 Hz, NCH$_2$C**H**HCH$_2$C), 1.68–1.42 (3H, m, NCH$_2$CH**H**CH$_2$C and NCH$_2$CH$_2$C**H**$_2$C).

^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*)

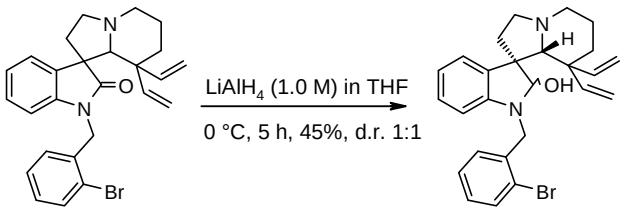
δ ppm 180.9 (**C**=O), 142.2 (**C**), 142.2 (**C**H), 141.7 (**C**H), 135.0 (**C**), 133.1 (**C**H), 132.9 (**C**), 129.1 (**C**H), 128.6 (**C**H), 128.0 (**C**H), 127.9 (**C**H), 127.8 (**C**H), 123.0 (**C**), 121.8 (**C**H), 115.1 (**C**H$_2$), 112.8 (**C**H$_2$), 108.8 (**C**H), 79.9 (**C**H), 56.0 (**C**), 55.2 (**C**H$_2$), 54.5 (**C**H$_2$), 46.5 (**C**), 44.3 (**C**H$_2$), 38.5 (**C**H$_2$), 37.3 (**C**H$_2$), 21.9 (**C**H$_2$).

^{1}H-^{1}H and ^{1}H-^{13}C correlations obtained to confirm above NMR assignments.

ESMS: *m/z* (%): 463:465 {1:1} $[M+H]^+$ Br^{79}:Br^{81} (100).

HRMS (ES +ve): $C_{26}H_{28}BrN_2O$ $[M+H]^+$ 463.1378, found 463.1380.

1′-(2-Bromo-benzyl)-2′-hyrdoxy-8,8-divinyl-octahydrospiro[indolizine1,3′-indol-2′-one] (355).



354
$C_{26}H_{27}BrN_2O$
(463.42)

355
$C_{26}H_{29}BrN_2O$
(465.44)

To a solution of oxindole **354** (0.32 mmol, 0.15 g) in anhydrous THF (20 mL) at 0 °C under nitrogen was added a solution of $LiAlH_4$ (1.0 M in THF, 0.36 mmol, 0.36 mL) drop-wise. After 5 h water (30 mL) was added cautiously. The reaction mixture was extracted with ether (3 x 30 mL) and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 1→20% MeOH in $CHCl_3$) to give **355** (0.14 mmol, 67 mg, 45%) as a brown oil.

Novel

IR (ATR / golden gate): 3293 (b w), 3062 (w), 3005 (w), 2930 (w), 2854 (w), 1712 (m), 1662 (m), 1610 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.68–7.63 (1H+1H, m, 2 x aromatic C**H**), 7.61 (1H+1H, m, 2 x aromatic C**H**), 7.24–7.09 (4H+4H, m, 2 x 4 x aromatic C**H**), 7.00 (1H+1H, m, 2 x aromatic C**H**), 6.59–6.53 (1H+1H, m, 2 x aromatic C**H**), 6.06 (1H, dd, *J*=17.8, 10.9 Hz, C**H**=CH_2), 5.96–5.82 (1H+2H, m, 3 x C**H**=CH_2), 5.357 (2H, s, NC**H**$_2$Ar), 5.353 (2H, s, NC**H**$_2$Ar) 5.26–4.97 (4H+4H, m, 2 x CH=C**H**$_2$), 4.32 (1H, s, NC**H**OH), 3.87 (1H, s, NC**H**OH), 3.46 (1H+1H, s, 2 x NC**H**), 3.10–2.90 (4H+4H, m, 2 x 2 x C**H**$_2$), 2.88–2.73 (1H+1H, m, 2 x C**H**H), 2.71–2.60 (1H+1H, m, 2 x CH**H**), 1.96–1.86

(1H+1H, m, 2 x C**H**H), 1.85–1.70 (1H+1H, m, 2 x CH**H**), 1.64–1.48 (2H+2H, m, 2 x C$\mathbf{H}_2$).

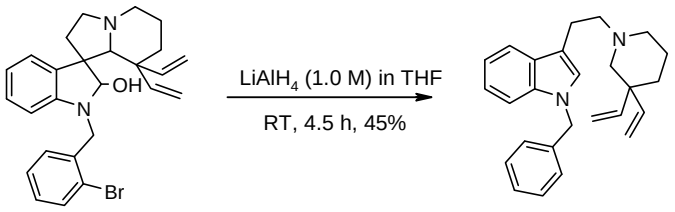
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 144.1+143.4 (**C**H), 142.6+142.4 (**C**H), 137.2+136.8 (**C**), 132.9 (**C**H), 129.1 (**C**H), 128.5 (**C**), 128.3+128.0 (**C**H), 126.3+126.1 (**C**H), 122.3 (**C**), 122.0 (**C**H), 119.4 (**C**H), 119.3 (**C**H), 115.1+114.8 (C$\mathbf{H}_2$), 114.6+113.1 (**C**H_2), 109.8+109.7 (**C**H), 98.3+87.3 (**C**H), 60.6 (**C**H), 55.9+55.2 (**C**H_2), 53.6+51.1 (**C**), 50.2 (**C**H_2), 48.7+48.4 (**C**), 45.2 (**C**H_2), 28.3+27.5 (**C**H_2), 24.1+23.8 (**C**H_2), 21.5 (**C**H_2).
N.B. 1 x aromatic (**C**) not observed.

^{1}H-^{1}H and ^{1}H-^{13}C correlations obtained to confirm above NMR assignments.

ESMS: *m/z* (%): 369 $[M\text{-}Br\text{-}OH]^+$ (100), 447:449 {1:1} $[M\text{-}OH]^+$ Br^{79}:Br^{81} (50).

1-Benzyl-3-[2-(3,3-divinyl-piperidin-1-yl)-ethyl]-1*H*-indole (357).



355
$C_{26}H_{29}BrN_2O$
(465.44)

357
$C_{26}H_{30}N_2$
(370.54)

To a solution of **355** (0.05 mmol, 23 mg) in anhydrous THF (10 mL) at 0 °C under argon, was added a solution of $LiAlH_4$ (1.0 M in THF, 0.15 mmol, 0.15 mL) dropwise. The reaction mixture was allowed to warm to room temperature and after 4.5 h was cooled to 0 °C and water (20 mL) was added cautiously. The aqueous phase was extracted with ether (4 x 20 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 30% diethyl ether in petroleum ether) to give indole **357** (0.02 mmol, 7 mg, 38%) as a pale brown oil.

Novel

IR (ATR / golden gate): 3085 (w), 3051 (w), 3032 (w), 2926 (w), 2862 (w), 2801 (w), 1716 (w), 1629 (w), 1618 (w), 1466 (w).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.63 (1H, d, *J*=7.7 Hz, aromatic C**H**), 7.33–7.23 (4H, m, 4 x aromatic C**H**), 7.17 (1H, app. td, *J*=7.5, 1.0 Hz, aromatic C**H**), 7.14–7.08 (3H, m, 3 x aromatic C**H**), 6.99 (1H, s, aromatic C**H**), 5.85 (2H, dd, *J*=17.5, 10.9 Hz, 2 x C**H**=CH_2), 5.28 (2H, s, NC$\mathbf{H}_2$Ph), 5.16–5.03 (4H, m, 2 x CH=C$\mathbf{H}_2$), 3.03–2.91 (2H, m, NC$\mathbf{H}_2$), 2.73–2.63 (2H, m, NC$\mathbf{H}_2$), 2.48 (4H, b s, 2 x NC$\mathbf{H}_2$ and C$\mathbf{H}_2$), 1.79–1.54 (4H, m, 2 x C$\mathbf{H}_2$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 144.4 (**C**H), 138.0 (**C**), 136.8 (**C**), 128.9 (2x**C**H), 128.5 (**C**), 127.7 (**C**H), 127.0 (2x**C**H), 126.0

(**C**H), 121.8 (**C**H), 119.3 (**C**H), 119.0 (**C**H), 113.6 (**C**H_2), 109.8 (**C**H), 62.6 (**C**H_2), 60.0 (**C**H_2), 54.9 (**C**H_2), 50.1 (**C**H_2), 43.6 (**C**), 33.8 (**C**H_2), 22.8 (**C**H_2), 22.5 (**C**H_2).

NB. 1 x aromatic (**C**) not observed.

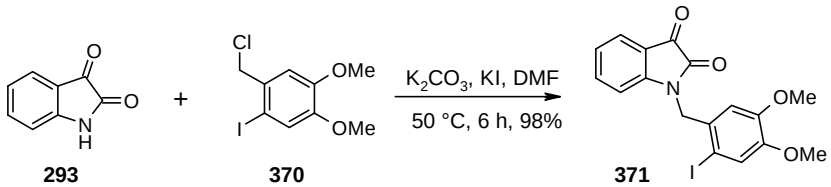
^{1}H-^{1}H and ^{1}H-^{13}C correlations obtained to confirm above NMR assignments.

ESMS: *m/z* (%): 371 $[M+H]^+$ (100).

HRMS (ES +ve): $C_{26}H_{31}N_2$ $[M+H]^+$ 371.2482, found 371.2477.

Synthetic Procedures–Chapter 4

1-(2-Iodo-4,5-dimethoxy-benzyl)-1*H*-indole-2,3-dione (371).



293 $C_8H_5NO_2$ (147.13)

370 $C_9H_{10}ClIO_2$ (312.54)

371 $C_{17}H_{14}INO_4$ (423.21)

A solution of isatin (**293**) (1.69 mmol, 0.25 g) and potassium carbonate (2.45 mmol, 0.34 g) in anhydrous DMF (10 mL) was stirred at 50 °C for 1 h under nitrogen. Potassium iodide (0.34 mmol, 56 mg) and a solution of benzyl chloride (**370**) (1.86 mmol, 0.58 g) in DMF (5 mL) were sequentially added. After 6 h the reaction mixture was cooled to room temperature and HCl (1M, 50 mL) added. The aqueous phase was extracted with ethyl acetate (2 x 40 mL) then the combined organic phasess were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the title product (**371**) (1.66 mmol, 0.70 g, 98%) as an orange solid. Data consistent with the literature.[78]

IR (ATR / golden gate): 3077 (w), 3003 (w), 2950 (w), 2909 (w), 2835 (w), 1733 (s), 1611 (s), 1503 (s), 1466 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

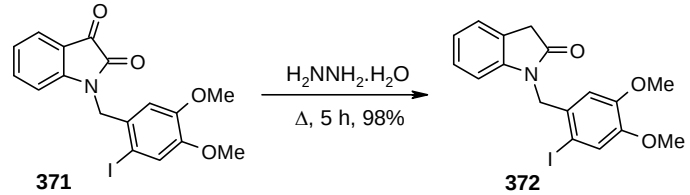
δ ppm 7.64 (1H, dd, *J*=7.5, 0.8 Hz, aromatic C**H**), 7.52 (1H, app. td, *J*=7.8, 1.5 Hz, aromatic C**H**), 7.30 (1H, s, aromatic C**H**), 7.12 (1H, app. td, *J*=7.5, 0.8 Hz, aromatic C**H**), 6.81 (1H, d, *J*=7.8 Hz, aromatic C**H**), 6.70 (1H, s, aromatic C**H**), 4.96 (2H, s, NC**H**$_2$Ar), 3.87 (3H, s, OC**H**$_3$), 3.72 (3H, s, OC**H**$_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 183.5 (**C**=O), 158.5 (**C**=O), 150.5 (**C**), 150.1 (**C**), 149.4 (**C**), 138.5 (**C**H), 128.7 (**C**), 125.4 (**C**H), 124.1 (**C**H), 121.7 (**C**H), 117.7 (**C**), 111.8 (**C**H), 110.6 (**C**H), 86.2 (**C**I), 56.2 (O**C**H$_3$), 56.0 (O**C**H$_3$), 48.9 (**C**H$_2$).

ESMS: *m/z* (%): 446 $[M+Na]^+$ (50), 870 $[M_2+Na]^+$ (100).

1-(2-Iodo-4,5-dimethoxy-benzyl)-1,3-dihydro-indol-2-one (372).



371
$C_{17}H_{14}INO_4$
(423.21)

372
$C_{17}H_{16}INO_3$
(409.23)

To hydrazine mono-hydrate (10 mL) was added **371** (1.66 mmol, 0.70 g). The reaction mixture was heated at reflux under nitrogen for 5 h then cooled to room temperature, and poured onto ice water (50 mL) and extracted with ethyl acetate (4 x 15 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 20% ethyl acetate in hexanes) to give **372** (1.64 mmol, 0.67 g, 98%) as a white solid.

Novel

Mpt: 189–190 °C (EtOAc in hexanes).

IR (ATR / golden gate): 2995 (w), 2962 (w), 2925 (w), 2835 (w), 1683 (s), 1614 (m), 1599 (m), 1505 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.30–7.23 (2H, m, 2 x aromatic C**H**), 7.18 (1H, app. t, *J*=7.7 Hz, aromatic C**H**), 7.03 (1H, app. t, *J*=7.6 Hz, aromatic C**H**), 6.72 (1H, d, *J*=7.7 Hz, aromatic C**H**), 6.62 (1H, s, aromatic C**H**), 4.91 (2H, s, NC**H**$_2$Ar), 3.89 (2H, s, NCOC**H**$_2$), 3.68 (3H, s, OC**H**$_3$), 3.67 (3H, s, OC**H**$_3$).

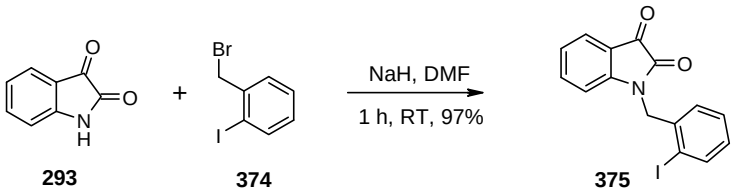
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 175.3 (**C**=O), 149.8 (**C**), 149.1 (**C**), 144.0 (**C**), 130.0 (**C**), 128.0 (**C**H), 124.4 (**C**H), 124.2 (**C**), 122.6 (**C**H), 121.6 (**C**H), 110.6 (**C**H), 109.7 (**C**H), 86.0 (**C**I), 56.1 (O**C**H$_3$), 55.9 (O**C**H$_3$), 48.5 (**C**H$_2$), 35.8 (**C**H$_2$).

ESMS: *m/z* (%): 303 $[(M-I)+Na]^+$ (60), 432 $[M+Na]^+$ (70).

HRMS (ES +ve): $C_{17}H_{16}INNaO_3$ $[M+Na]^+$ 432.0067, found 432.0070.

1-(2-Iodo-benzyl)-1*H*-indole-2,3-dione (375).



293
$C_8H_5NO_2$
(147.13)

374
C_7H_6BrI
(296.93)

375
$C_{15}H_{10}INO_2$
(363.16)

To a solution of isatin (**293**) (1.36 mmol, 0.20 g) in anhydrous DMF (20 mL) under nitrogen at room temperature was added NaH (60% dispersion in mineral oil, 11.50 mmol, 60 mg). After 30 min 2-iodobenzyl bromide (**374**) (1.50 mmol, 0.45 g) was added followed after 1 h by water (60 mL). The reaction mixture was extracted with ethyl acetate (2 x 40 mL). The combined organic phases were washed with water (3 x 50 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give the title product **375** (1.30 mmol, 0.48 g, 97%) as an orange solid.

Novel

Mpt: 155–158 °C (EtOAc in hexanes).

IR (ATR / golden gate): 2954 (w), 2921 (w), 2852 (w), 1733 (s), 1605 (s), 1460 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.91 (1H, dd, *J*=8.0, 1.1 Hz, aromatic C**H**), 7.67 (1H, ddd, *J*=7.6, 1.4, 0.6 Hz, aromatic C**H**), 7.51 (1H, app. td, *J*=7.7, 1.4 Hz, aromatic C**H**), 7.30 (1H, app. td, *J*=7.7, 1.1 Hz, aromatic C**H**), 7.17–7.09 (2H, m, 2 x aromatic C**H**), 7.02 (1H, app. td, *J*=7.6, 1.7 Hz, aromatic C**H**), 6.69 (1H, d, *J*=8.0 Hz, aromatic C**H**), 4.99 (2H, s, NC**H**$_2$Ar).

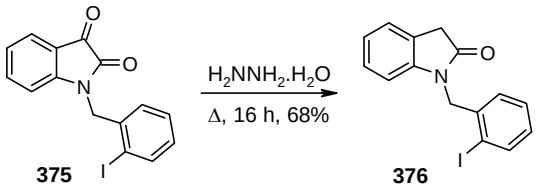
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 174.8 (**C**=O), 158.5 (**C**=O), 150.6 (**C**), 140.1 (**C**H), 138.7 (**C**H), 136.2 (**C**), 129.9 (**C**H), 129.1(**C**H), 127.3 (**C**H), 125.7 (**C**H), 124.3 (**C**H), 118.0 (**C**), 111.5 (**C**H), 97.8 (**C**I), 49.4 (**C**H$_2$).

ESMS: *m/z* (%): 386 $[M+Na]^+$ (100).

HRMS (ES +ve): $C_{15}H_{10}INNaO_2$ $[M+Na]^+$ 385.9648, found 385.9649.

1-(2-Iodo-benzyl)-1,3-dihydro-indol-2-one (376).



375
$C_{15}H_{10}INO_2$
(363.16)

376
$C_{15}H_{12}INO$
(349.17)

To hydrazine mono-hydrate (10 mL) was added **375** (1.52 mmol, 0.55 g). The reaction mixture was heated at reflux under nitrogen for 16h then cooled to room temperature, poured onto ice water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 30% ethyl acetate in hexanes) to give **376** (1.04 mmol, 0.36 g, 68%) as a brown solid.

Novel

Mpt: 99–102 °C (EtOAc in hexanes).

IR (ATR / golden gate): 3056 (w), 3019 (w), 2978 (w), 2958 (w), 2942 (w), 2917 (w), 1687 (s), 1612 (s), 1495 (m), 1465 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.87 (1H, d, *J*=8.1 Hz, aromatic C**H**), 7.22 (3H, m, 3 x aromatic C**H**), 6.99 (3H, m, 3 x aromatic C**H**), 6.60 (1H, d, *J*=7.7 Hz, aromatic C**H**), 4.92 (2H, s, NC**H**$_2$Ar), 3.68 (2H, s, NCOC**H**$_2$).

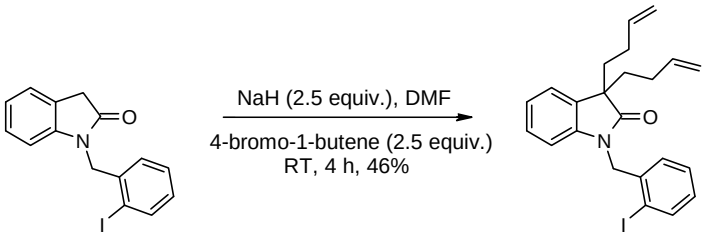
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 175.2 (**C**=O), 144.0 (**C**), 139.6 (**C**H), 137.2 (**C**), 129.2 (**C**H), 128.6 (**C**H), 128.0 (**C**H), 127.0 (**C**H), 124.5 (**C**H), 124.3 (**C**), 122.7 (**C**H), 109.3 (**C**H), 97.7 (**C**I), 48.9 (**C**H$_2$), 35.9 (**C**H$_2$).

ESMS: *m/z* (%): 372 $[M+Na]^+$ (100), 721 $[M_2+Na]^+$ (80).

HRMS (ES +ve): $C_{15}H_{12}INNaO$ $[M+Na]^+$ 371.9856, found 371.9855.

3,3-Di-but-3-enyl-1-(2-iodo-benzyl)-1,3-dihydro-indol-2-one (377).



376
$C_{15}H_{12}INO$
(349.17)

377
$C_{23}H_{24}INO$
(457.36)

To a solution of oxindole (**376**) (2.29 mmol, 0.80 g) in anhydrous DMF (50 mL) at room temperature under nitrogen was added sodium hydride (60% in mineral oil, 5.73 mmol, 0.23 g). After 30 min a solution of 4-bromo-1-butene (5.73 mmol, 0.58 mL) in anhydrous DMF (3 mL) was added followed after 4 h with water (50 mL). The reaction mixture was extracted with ethyl acetate (2 x 40 mL) and then the combined organic phases were washed with water (4 x 30 mL), brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 2% ethyl acetate in hexanes) to give the desired *bis*-alkylated material (**377**) (1.05 mmol, 0.48 g, 46%) as a white solid.

Novel

Mpt: 93–96 °C (EtOH).

IR (ATR / golden gate): 3060 (w), 3036 (w), 2970 (w), 2913 (w), 2840 (w), 1705 (s), 1638 (w), 1611 (m), 1487 (m), 1465 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.88 (1H, dd, *J*=8.2, 1.3 Hz, aromatic C**H**), 7.27–7.13 (4H, m, 4 x aromatic C**H**), 7.09 (1H, app. td, *J*=7.6, 1.0 Hz, aromatic C**H**), 6.97 (1H, d, *J*=7.4 Hz, aromatic C**H**), 6.62 (1H, d, *J*=7.6 Hz, aromatic C**H**), 5.75–5.62 (2H, m, 2 x C**H**=CH_2), 4.94–4.84 (6H, m, 2 x CH=C**H**$_2$ and NC**H**$_2$Ar), 2.16–2.02 (2H, m, 2 x C**H**H), 1.97–1.81 (4H, m, 4 x CH**H**), 1.78–1.63 (2H, m, 2 x C**H**H).

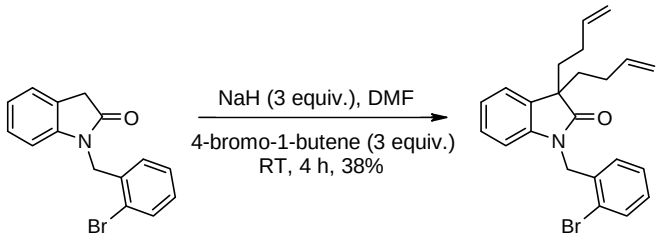
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 179.8 (**C**=O), 143.0 (**C**), 139.6 (**C**H), 137.6 (2x**C**H), 137.4 (**C**), 131.6 (**C**), 129.1 (**C**H), 128.5 (**C**H), 127.9 (**C**H), 127.0 (**C**H), 122.9 (**C**H), 122.8 (**C**H), 114.8 (2x**C**H_2), 109.2 (**C**H), 97.8 (**C**I), 52.6 (**C**), 49.1 (**C**H_2), 37.4 (2x**C**H_2), 28.7 (2x**C**H_2).

ESMS: *m/z* (%): 458 $[M+H]^+$ (100), 480 $[M+Na]^+$ (40).

HRMS (ES +ve): $C_{23}H_{24}INNaO$ $[M+Na]^+$ 480.0795, found 480.0797.

1-(2-Bromo-benzyl)-3,3-di-but-3-enyl-1,3-dihydro-indol-2-one (378).



352
$C_{15}H_{12}BrNO$
(302.17)

378
$C_{23}H_{24}BrNO$
(410.36)

To a solution of oxindole (**352**) (1.99 mmol, 0.60 g) in anhydrous DMF (50 mL) at room temperature under nitrogen was added sodium hydride (60% in mineral oil, 5.96 mmol, 0.24 g). After 30 min a solution of 4-bromo-1-butene (5.96 mmol, 0.61 mL) in anhydrous DMF (3 mL) was added followed after 4 h by water (100 mL). The reaction mixture extracted with ethyl acetate (2 x 50 mL), then the combined organic phases were washed with water (4 x 50 mL), brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 2% ethyl acetate in hexanes) to give desired *bis*-alkylated material (**378**) (0.76 mmol, 0.31 g, 38%) as a pink solid.

Novel

Mpt: 115–116°C (EtOH).

IR (ATR / golden gate): 3068 (w), 3007 (w), 2978 (w), 2933 (w), 2905 (w), 2835 (w), 1705 (s), 1638 (w), 1613 (m), 1487 (m), 1464 (m), 1444 (m).

^{1}H NMR (400 MHz, CHLOROFORM-*d*)

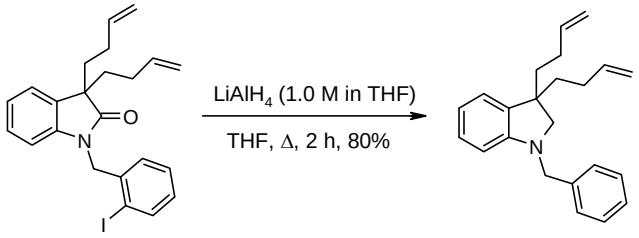
δ ppm 7.60 (1H, dd, *J*=7.9, 1.3 Hz, aromatic C**H**), 7.23–7.02 (6H, m, 6 x aromatic C**H**), 6.68 (1H, d, *J*=7.7 Hz, aromatic C**H**), 5.75–5.61 (2H, m, 2 x C**H**=CH_2), 5.01 (2H, s, NC**H**$_2$Ar), 4.93–4.84 (4H, m, 2 x CH=C**H**$_2$), 2.14–2.03 (2H, m, 2 x C**H**H), 1.97–1.79 (4H, m, 4 x CH**H**), 1.77–1.63 (2H, m, 2 x C**H**H).

^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*)

δ ppm 180.0 (**C**=O), 143.2 (**C**), 137.9 (2x**C**H), 135.0 (**C**), 133.2 (**C**H), 131.9 (**C**), 129.2 (**C**H), 128.2 (**C**H),

	128.0 (**C**H), 127.9 (**C**H), 123.1 (**C**H), 123.0 (**C**), 123.0 (**C**H), 115.0 (2x**C**H_2), 109.3 (**C**H), 52.8 (**C**), 44.1 (**C**H_2), 37.6 (2x**C**H_2), 28.9 (2x**C**H_2).
CIMS: *m/z* (%):	410:412 {1:1} $[M+H]^{+\cdot}$ Br^{79}:Br^{81} (100), 355:357 $[(M-CH_2CH_2CHCH_2)+H]^{+\cdot}$ Br^{79}:Br^{81} (20), 332 $[(M-Br)+H]^{+\cdot}$ (30), 316 (40), 277 (10), 234 (20), 171 (20), 91 (20).
HRMS (ES +ve):	$C_{23}H_{24}BrNNaO$ $[M+Na]^+$ 432.0933, found 432.0932.

1-Benzyl-3,3-di-but-3-enyl-2,3-dihydro-1*H*-indole (379).



377
$C_{23}H_{24}INO$
(457.36)

379
$C_{23}H_{27}N$
(317.48)

To a solution of $LiAlH_4$ (1.0 M solution in THF, 3.13 mmol, 3.13 mL) in anhydrous THF (25 mL) at 0 ºC under nitrogen was added a solution of oxindole (**377**) (1.04 mmol, 0.48 g) in anhydrous THF (20 mL) drop-wise. The reaction was heated at reflux for 2 h then cooled to 0 ºC and water (50 mL) added slowly. The mixture was extracted with ethyl acetate (3 x 30 mL), then the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 1% ethyl acetate in hexanes) to give indoline (**379**) (0.83 mmol, 0.26 g, 80%) as a yellow oil.

Novel

IR (ATR / golden gate): 3072 (w), 3032 (w), 2921 (m), 2848 (m), 1638 (m), 1603 (m), 1489 (m), 1453 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.35–7.22 (5H, m, 5 x aromatic C**H**), 7.06 (1H, ddd, *J*=7.9, 7.6, 1.0 Hz, aromatic C**H**), 6.97 (1H, d, *J*=7.9 Hz, aromatic C**H**), 6.67 (1H, app. td, *J*=7.6, 1.0 Hz, aromatic C**H**), 6.48 (1H, d, *J*=7.6 Hz, aromatic C**H**), 5.83–5.70 (2H, m, 2 x C**H**=CH_2), 4.96 (2 H, dd, *J*=17.3, 1.7 Hz, 2 x CH=C**H**H), 4.90 (2H, d, *J*=10.4 Hz, 2 x CH=CH**H**), 4.26 (2H, s, NC**H**$_2$Ar), 3.16 (2H, s, NC**H**$_2$), 2.00-2.10 (2H, m, 2 x C**H**H), 1.84-1.91 (2H, m, 2 x C**H**H), 1.77 (2H, td, *J*=13.4, 4.6 Hz, 2 x CH**H**), 1.65 (2H, td, *J*=12.6, 4.4 Hz, 2 x CH**H**).

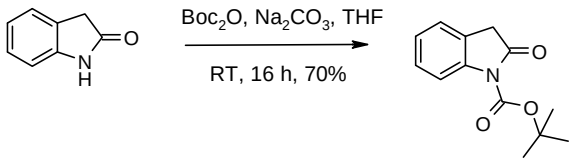
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 152.0 (**C**), 138.9 (2x**C**H), 138.5 (**C**), 135.3 (**C**), 128.6 (**C**H), 128.5 (2x**C**H), 127.1 (2x**C**H), 127.1 (**C**H), 123.1 (**C**H), 117.3 (**C**H), 114.2 (2x**C**H_2), 106.7 (**C**H), 63.6 (**C**H_2), 53.1 (**C**H_2), 46.9 (**C**), 38.2 (2x**C**H_2), 28.8 (2x**C**H_2).

CIMS: *m/z* (%): 318 $[M+H]^{+\cdot}$ (100), 262 (30), 220 (30), 172 (25), 130 (30), 106 (35), 91 (70).

HRMS (ES +ve): $C_{23}H_{28}N$ $[M+H]^+$ 318.2216, found 318.2218.

***tert*-Butyl 2-Oxo-2,3-dihydro-indole-1-carboxylate (381).**



251
C_8H_7NO
(133.15)

381
$C_{13}H_{15}NO_3$
(233.27)

To a solution of oxindole (**251**) (3.76 mmol, 0.50 g) in anhydrous THF (30 mL) at room temperature under nitrogen, was added di-*tert*-butyl dicarbonate (9.39 mmol, 2.05 g), and sodium carbonate (36.3 mmol, 2.79 g). after 16 h the reaction mixture was filtered, concentrated *in vacuo* and purified by column chromatography (silica, 20% diethyl ether in petroleum ether) to give the *N*-Boc material (**381**) as a white solid (2.59 mmol, 0.61 g, 70%). Data consistent with the literature.[79]

IR (ATR / golden gate): 3052 (w), 2987 (w), 2950 (w), 2925 (w), 1787 (s), 1760 (s), 1719 (s).

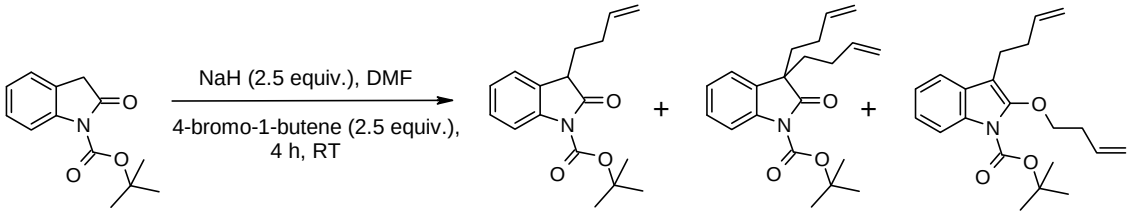
^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.79 (1H, d, *J*=8.1 Hz, aromatic C**H**), 7.35–7.21 (2H, m, 2 x aromatic C**H**), 7.14 (1H, app. td, *J*=7.5, 0.9 Hz, aromatic C**H**), 3.65 (2H, s, COC**H**$_2$), 1.65 (9H, s, COOC(C**H**$_3$)$_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 173.2 (**C**=O), 149.4 (**C**=O), 141.2 (**C**), 128.2 (**C**H), 124.3 (2x**C**H), 123.4 (**C**), 115.2 (**C**H), 84.5 (**C**), 36.7 (**C**H$_2$), 28.3 (3x**C**H$_3$).

***tert*-Butyl 3,3-di-but-3-enyl-2-oxo-2,3-dihydro-indole-1-carboxylate (383), *tert*-Butyl 3-but-3-enyl-2-oxo-2,3-dihydro-indole-1-carboxylate (382) and *tert*-Butyl 3-but-3-enyl-2-but-3-enyloxy-indole-1-carboxylate (384).**



383
$C_{13}H_{15}NO_3$
(233.27)

382, 20%
$C_{17}H_{21}NO_3$
(287.36)

383, 44%
$C_{21}H_{27}NO_3$
(341.45)

384, 3%
$C_{21}H_{27}NO_3$
(341.45)

To a solution of Boc-oxindole (**383**) (6.43 mmol, 1.50 g) in anhydrous DMF (130 mL) at 0 ºC under nitrogen was added sodium hydride (60% in mineral oil, 19.29 mmol, 0.77 g). After 1 h 4-bromo-1-butene (19.29 mmol, 1.96 mL) was added drop-wise followed, after 4 h at 0 ºC and 3 h at room temperature, by water (200 mL). The reaction mixture was extracted with ether (2 x 100 mL), then the combined organic phases were washed with water (3 x 100 mL), brine (200 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 10% diethyl ether in petroleum ether) to firstly give o-alkylated material (**384**) (0.16 mmol, 55 mg, 3%), followed by the desired *bis*-alkylated material (**383**) (2.82 mmol, 0.96 g, 44%) and then the *mono*-alkylated material (**382**) (1.31 mmol, 0.38 g, 20%) all as a clear oils.

Data for **382**

Novel

IR (ATR / golden gate): 3077 (w), 2978 (w), 2925 (w), 1793 (m), 1764 (s), 1727 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.82 (1H, d, *J*=8.4 Hz, aromatic C**H**), 7.35–7.22 (2H, m, 2 x aromatic C**H**), 7.16 (1H, app. dt, *J*=7.3, 1.1 Hz, aromatic C**H**), 5.80 (1H, m, C**H**=CH_2), 4.94–5.06 (2H, m, CH=C**H**$_2$), 3.58 (1H, t, *J*=5.5 Hz, C**H**$CH_2CH_2CH=CH_2$), 2.24–2.04 (4H, m, $CHCH_2CH_2CH=CH_2$), 1.65 (9H, s, $CO_2C(CH_3)_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 176.1 (**C**=O), 149.3 (**C**=O), 140.2 (**C**), 137.2 (**C**H), 128.1 (**C**H), 127.8 (**C**), 124.2 (**C**H), 123.6 (**C**H), 115.7 (**C**H_2), 114.9 (**C**H), 84.2 (**C**), 45.2 (**C**H), 30.4 (**C**H_2), 29.8 (**C**H_2), 28.1 (3x**C**H_3).

ESMS: *m/z* (%): 232 $[M-{}^{t}Bu+H]^+$ (70), 310 $[M+Na]^+$ (20), 560 $[M_2+Na]^+$ (100).

HRMS (ES +ve): $C_{17}H_{21}NNaO_3$ $[M+Na]^+$ 310.1419, found 310.1414.

Data for **383**

Novel

IR (ATR / golden gate): 3072 (w), 2978 (w), 2933 (w), 2909 (w), 2848 (w), 1973 (w), 1763 (m), 1727 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.83 (1H, d, *J*=8.1 Hz, aromatic C**H**), 7.31 (1H, ddd, *J*=8.1, 7.4, 1.8 Hz, aromatic C**H**), 7.20 (1H, app. td, *J*=7.4, 1.0 Hz, aromatic C**H**), 7.16 (1H, ddd, *J*=7.4, 1.8, 1.0 Hz, aromatic C**H**), 5.64 (2H, m, 2 x C**H**=CH_2), 4.90–4.80 (4H, m, 2 x CH=C**H**$_2$), 2.14–2.00 (2H, m, 2 x C**H**H), 1.90–1.67 (6H, m, 2 x C**H**H and 4 x CH**H**), 1.65 (9H, s, OC(C**H**$_3$)$_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 178.4 (**C**=O), 149.1 (**C**=O), 140.0 (**C**), 137.3 (2x**C**H), 130.6 (**C**), 128.1 (**C**H), 124.5 (**C**H), 122.6 (**C**H), 114.9 (2x**C**H_2), 114.9 (**C**H) 84.2 (**C**), 52.8 (**C**), 38.1 (2x**C**H_2), 28.6 (2x**C**H_2), 28.1 (3x**C**H_3).

ESMS: *m/z* (%): 286 $[M-{}^{t}Bu+H]^+$ (50), 364 $[M+Na]^+$ (30), 706 $[M_2+Na]^+$ (100).

HRMS (ES +ve): $C_{21}H_{27}NNaO_3$ $[M+Na]^+$ 364.1889, found 364.1883.

Data for **384**

Novel

IR (ATR / golden gate): 3081 (w), 2970 (w), 2929 (w), 2852 (w), 1727 (m), 1618 (m), 1458 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

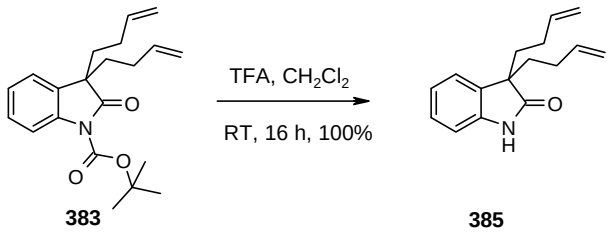
δ ppm 8.04 (1H, m, aromatic C**H**), 7.44 (1H, m, aromatic C**H**), 7.26–7.20 (2H, m, 2 x aromatic C**H**), 6.03–5.84 (2H, m, 2 x C**H**=CH_2), 5.25–4.97 (4H, m, 2 x CH=C**H**$_2$), 4.13 (2H, t, *J*=6.9 Hz, OC**H**$_2$$CH_2$CH=$CH_2$), 2.73 (2H, dd, *J*=10.0, 7.5 Hz, C**H**$_2$$CH_2$CH=$CH_2$), 2.60 (2H, app. qt, *J*=6.9, 1.3 Hz, OCH_2C**H**$_2$CH=CH_2), 2.46–2.36 (2H, m, CH_2C**H**$_2$CH=CH_2), 1.70 (9H, s, C(C**H**$_3$)$_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 149.5 (**C**=O), 147.7 (**C**), 138.5 (**C**H), 134.4 (**C**H), 132.1 (**C**), 128.3 (**C**), 123.3 (**C**H), 122.7 (**C**H), 118.4 (**C**H), 117.5 (**C**H_2), 115.4 (**C**H), 115.1 (**C**H_2), 105.3 (**C**), 83.7 (**C**), 75.6 (**C**H_2), 34.4 (**C**H_2), 33.9 (**C**H_2), 28.5 (3x**C**H_3), 22.6 (**C**H_2).

ESMS: *m/z* (%): 286 $[M-{}^{t}Bu+H]^+$ (100), 342 $[M+H]^+$ (20), 364 $[M+Na]^+$ (70), 706 $[M_2+Na]^+$ (40).

3,3-Di-but-3-enyl-1,3-dihydro-indol-2-one (385).



383
$C_{21}H_{27}NO_3$
(341.45)

385
$C_{16}H_{19}NO$
(241.34)

To a solution of oxindole (**383**) (2.78 mmol, 0.95 g) in dichloromethane (50 mL) under nitrogen at 0 ºC was added TFA (2.5 mL). The reaction mixture was allowed to warm to room temperature slowly and after 16 h was concentrated *in vacuo* to give oxindole (**385**) as a yellow oil (2.78 mmol, 0.67 g, 100%).

Novel

IR (ATR / golden gate): 3162 (w), 3085 (w), 2974 (w), 2929 (w), 2844 (w), 1709 (s), 1668 (s), 1642 (s), 1619 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 9.25 (1H, b s, N**H**), 7.29 (1H, ddd, *J*=7.7, 7.1, 1.8 Hz, aromatic C**H**), 7.25-7.20 (2H, m, 2 x aromatic C**H**), 7.15 (1H, app. dt, *J*=7.1, 1.0 Hz, aromatic C**H**), 5.66 (2H, ddt, *J*=16.1, 11.1, 6.3 Hz, 2 x CH_2=C**H**), 4.95–4.83 (4H, m, 2 x C**H**$_2$=CH), 2.11–1.60 (8H, m, 2 x CH_2=CHC**H**$_2$C**H**$_2$).

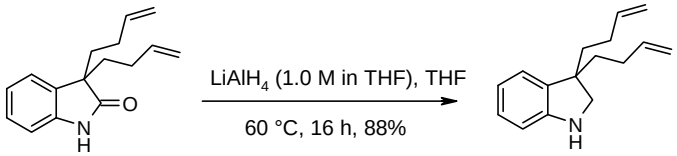
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 184.8 (**C**=O), 140.2 (**C**), 137.2 (2x**C**H), 132.1 (**C**), 128.2 (**C**H), 123.6 (**C**H), 123.2 (**C**H), 115.1 (2x**C**H_2), 110.6 (**C**H), 54.0 (**C**), 36.9 (2x**C**H_2), 28.4 (2x**C**H_2).

CIMS: *m/z* (%): 242 $[M+H]^{+\cdot}$ (100), 187 $[M\text{-}CH_2CH_2CHCH_2]^{+\cdot}$ (75), 146 (70), 130 (10), 117 (15).

HRMS (ES +ve): $C_{16}H_{19}NNaO$ $[M+Na]^+$ 264.1364, found 264.1359.

3,3-Di-but-3-enyl-2,3-dihydro-1*H*-indole (386).



385
$C_{16}H_{19}NO$
(241.34)

386
$C_{16}H_{21}N$
(227.35)

A solution of $LiAlH_4$ (1.0 M solution in THF, 7.71 mmol, 7.71 mL) was diluted with anhydrous THF (80 mL) and cooled to 0 ºC under nitrogen. A solution of oxindole (**385**) (2.57 mmol, 0.62 g) in anhydrous THF (20 mL) was added drop-wise and the reaction mixture heated to 70 ºC for 16 h then cooled to 0 ºC. Water (100 mL) was added cautiously, and then the reaction mixture was extracted with ether (3 x 50 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give indoline (**386**) as a brown oil (2.27 mmol, 0.52 g, 88%).

Novel

IR (ATR / golden gate): 3391 (w), 3072 (w), 2983 (w), 2921 (w), 2844 (w), 1642 (m), 1607 (m), 1487 (m), 1462 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

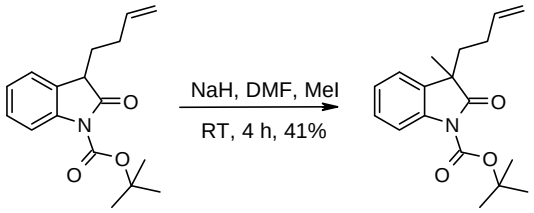
δ ppm 7.05 (1H, app. td, *J*=7.7, 1.3 Hz, aromatic C**H**), 7.00 (1H, dd, *J*=7.3, 0.7 Hz, aromatic C**H**), 6.74 (1H, app. td, *J*=7.3, 1.3 Hz, aromatic C**H**), 6.64 (1H, d, *J*=7.7 Hz, aromatic C**H**), 5.80 (2H, ddt, *J*=17.1, 10.3, 6.4 Hz, 2 x C**H**=CH_2), 5.05–4.96 (2H, m, 2 x CH=C**H**H), 4.93 (2H, d with fine splitting, *J*=10.3 Hz, 2 x CH=CH**H**), 3.41 (2H, s, NC**H**$_2$), 2.19–2.03 (2H, m, 2 x C**H**H), 2.01–1.86 (2H, m, 2 x CH**H**), 1.86–1.64 (4H, m, 2 x C**H**$_2$$CH_2$$CH$=$CH_2$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 151.2 (**C**), 138.9 (2x**C**H), 134.8 (**C**), 127.5 (**C**H), 123.3 (**C**H), 118.4 (**C**H), 114.2 (2x**C**H_2), 109.5

	(**C**H), 57.3 (**C**H_2), 48.5 (**C**), 38.1 (2x**C**H_2), 28.8 (2x**C**H_2).
CIMS: *m/z* (%):	228 $[M+H]^{+\cdot}$ (70), 172 $[M-CH_2CH_2CHCH_2]^{+\cdot}$ (50), 130 $[M-(CH_2CH_2CHCH_2)-(CH_2CHCH_2)]^{+\cdot}$ (100), 117 (10).
HRMS (EI):	$C_{16}H_{22}N$ $[M]^+$ 228.1752, found 228.1747.

***tert*-Butyl 3-but-3-enyl-3-methyl-2-oxo-2,3-dihydro-indole-1-carboxylate (387).**



382
$C_{17}H_{21}NO_3$
(287.36)

387
$C_{18}H_{23}NO_3$
(301.39)

To a solution of Boc-oxindole (**382**) (1.04 mmol, 0.30 g) in anhydrous DMF (30 mL) at 0 ºC under nitrogen was added sodium hydride (60% in mineral oil, 1.57 mmol, 63 mg). After 1.5 h methyl iodide (1.57 mmol, 0.1 mL) wad added drop-wise and warmed to room temperature for 4 h. Water (50 mL) was added and the reaction mixture extracted with ether (2 x 40 mL). The combined organic phases were washed with water (4 x 40 mL) and brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 5% diethyl ether in petroleum ether) to give the title compound **387** (0.42 mmol, 0.13 g, 41%) as a colourless oil.

Novel

IR (ATR / golden gate): 2974 (w), 2933 (w), 1789 (w), 1764 (m), 1727 (s), 1646 (w), 1610 (w), 1479 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.85 (1H, d, *J*=8.4 Hz, aromatic C**H**), 7.31 (1H, m, aromatic C**H**), 7.21–7.16 (2H, m, 2 x aromatic C**H**), 5.66 (1H, ddt, *J*=17.6, 9.6, 6.4 Hz, C**H**=CH_2), 4.91–4.82 (2H, m, CH=C**H**$_2$), 2.08 (1H, m, CH_2C**H**HCH=CH_2), 1.90–1.68 (3H, m, C**H**$_2$CH**H**CH=CH_2), 1.66 (9H, s, $CO_2C(CH_3)_3$), 1.43 (3H, s, C**H**$_3$).

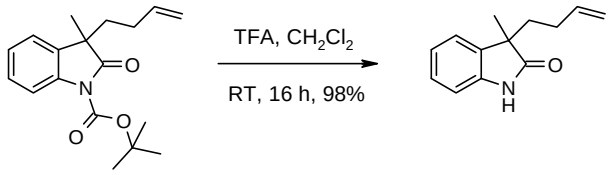
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 179.1 (**C**=O), 149.3 (**C**=O), 139.2 (**C**), 137.3 (**C**H), 132.6 (**C**), 128.0 (**C**H), 124.5 (**C**H), 122.4 (**C**H), 115.0 (**C**H), 114.9 (**C**H$_2$), 84.2 (**C**), 48.5 (**C**), 38.4 (**C**H$_2$), 28.9 (**C**H$_2$), 28.1 (3x**C**H$_3$), 24.9 (**C**H$_3$).

ESMS: *m/z* (%): 246 $[M-{}^{t}Bu]^+$ (80), 324 $[M+Na]^+$ (30), 626 $[M_2+Na]^+$ (100).

HRMS (ES +ve): $C_{18}H_{23}NNaO_3$ $[M+Na]^+$ 324.1570, found 324.1566.

3-But-3-enyl-3-methyl-1,3-dihydro-indol-2-one (388).



387
$C_{18}H_{23}NO_3$
(301.39)

388
$C_{13}H_{15}NO$
(201.27)

To a solution of oxindole (**387**) (0.42 mmol, 0.13 g) in dichloromethane (30 mL) under nitrogen at 0 ºC was added TFA (1.5 mL). The reaction mixture was allowed to warm to room temperature slowly and after 16 h was concentrated *in vacuo* to give oxindole (**388**) (0.41 mmol, 83 mg, 98%) as a yellow oil.

Novel

IR (ATR / golden gate): 3220 (b, w), 3072 (w), 3023 (w), 2974 (w), 2925 (w), 2844 (w), 1700 (s), 1620 (m), 1471 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 8.63 (1H, b s, N**H**), 7.23 (1H, app. td, *J*=7.7, 1.2 Hz, aromatic C**H**), 7.18 (1H, dd, *J*=7.5, 1.2 Hz, aromatic C**H**), 7.09 (1H, app. td, *J*=7.5, 0.7 Hz, aromatic C**H**), 6.94 (1H, d, *J*=7.7 Hz, aromatic C**H**), 5.68 (1H, m, C**H**=CH_2), 4.96–4.84 (2H, m, CH=C**H**$_2$), 2.13–1.61 (4H, m, C**H**$_2$C**H**$_2$CH=CH_2), 1.42 (3H, s, C**H**$_3$).

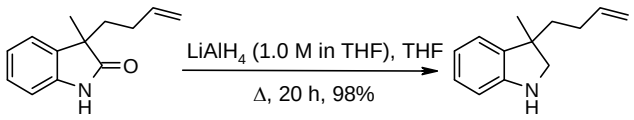
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 157.7 (**C**=O), 140.2 (**C**), 137.7 (**C**H), 134.5 (**C**), 128.1 (**C**H), 123.2 (**C**H), 123.1 (**C**H), 115.1 (**C**H_2), 110.2 (**C**H), 47.2 (**C**), 37.5 (**C**H_2), 29.0 (**C**H_2), 24.0 (**C**H_3).

CIMS: *m/z* (%): 202 $[M+H]^{+\cdot}$ (90), 147 $[M\text{-}CH_2CH_2CHCH_2]^{+\cdot}$ (100), 117 (10), 91 (5).

HRMS (ES +ve): $C_{13}H_{15}NNaO$ $[M+Na]^+$ 224.1046, found 224.1044.

3-But-3-enyl-3-methyl-2,3-dihydro-1*H*-indole (389).



388
$C_{13}H_{15}NO$
(201.27)

389
$C_{13}H_{17}N$
(187.29)

A solution of $LiAlH_4$ (1.0 M solution in THF, 1.23 mmol, 1.23 mL) was diluted with anhydrous THF (10 mL) and cooled to 0 ºC under nitrogen. A solution of oxindole (**388**) (0.41 mmol, 83 mg) in anhydrous THF (2 mL) was added drop-wise and the reaction mixture heated to 70 ºC for 20 h then cooled to 0 ºC. Water (20 mL) was added cautiously and the reaction mixture was extracted with ether (3 x 20 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give indoline (**389**) (0.40 mmol, 75 mg, 98%) as a yellow oil.

Novel

IR (ATR / golden gate): 3387 (w), 2958 (m), 2922 (m), 2856 (m), 1642 (w), 1605 (m), 1487 (m), 1462 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.08–7.00 (2H, m, 2 x aromatic C**H**), 6.75 (1H, app. td, *J*=7.5, 1.0 Hz, aromatic C**H**), 6.65 (1H, app. dt, *J*=7.5, 0.8 Hz, aromatic C**H**), 5.81 (1H, ddt, *J*=17.0, 10.3, 6.5 Hz, C**H**=CH_2), 5.01 (1H, app. dq, *J*=17.0, 1.8 Hz, CH=C**H**H), 4.93 (1H, app. ddt, *J*=10.3, 1.8, 1.3 Hz, CH=CH**H**), 3.44 (1H, d, *J*=8.9 Hz, NC**H**H), 3.28 (1H, d, *J*=8.9 Hz, NCH**H**), 2.22–1.89 (2H, m, 2 x C**H**H), 1.82–1.62 (2H, m, 2 x CH**H**), 1.33 (3H, s, C**H**$_3$).

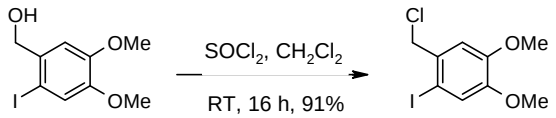
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 150.8 (**C**), 139.2 (**C**H), 137.1 (**C**), 127.6 (**C**H), 122.8 (**C**H), 118.8 (**C**H), 114.3 (**C**H_2), 109.8 (**C**H), 59.6 (**C**H_2), 45.2 (**C**), 40.0 (**C**H_2), 29.3 (**C**H_2), 26.0 (**C**H_3).

CIMS: *m/z* (%): 188 $[M+H]^{+\cdot}$ (100), 172 (10), 132 $[M-CH_2CH_2CH=CH_2]^{+\cdot}$ (100), 144 (15), 117 (15).

HRMS (ES +ve): $C_{13}H_{18}N$ $[M+H]^+$ 188.1434, found 188.1433.

1-Chloromethyl-2-iodo-4,5-dimethoxy-benzene (392).



391
$C_9H_{11}IO_3$
(294.09)

392
$C_9H_{10}ClIO_2$
(312.54)

To a solution of benzyl alcohol (**391**) (5.10 mmol, 1.50 g) in dichloromethane (50 mL), at 0 ºC under nitrogen, was added thionyl chloride (5.10 mmol, 0.37 mL) drop-wise. After 6 h at room temperature the reaction mixture was concentrated *in vacuo* to give the benzyl chloride (**392**) as a green solid (4.63 mmol, 1.45 g, 91%). Data consistent with the literature.[80]

IR (ATR / golden gate): 3003 (w), 2950 (w), 2929 (w), 2827 (w), 1594 (m), 1503 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

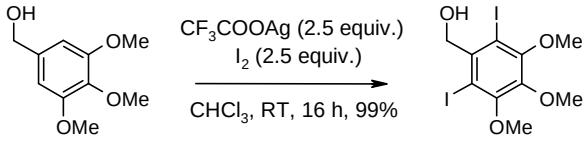
δ ppm 7.25 (1H, s, aromatic C**H**), 6.99 (1H, s, aromatic C**H**), 4.66 (2H, s, C**H**$_2$Cl), 3.89 (3H, s, OC**H**$_3$), 3.88 (3H, s, OC**H**$_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

δ ppm 150.0 (**C**), 132.7 (2x**C**), 122.2 (**C**H), 113.2 (**C**H), 88.3 (**C**I), 56.6 (O**C**H$_3$), 56.4 (O**C**H$_3$), 51.7 (**C**H$_2$).

EIMS: *m/z* (%): 312 $[M]^{+\cdot}$ (45), 277 $[M-Cl]^{+\cdot}$ (100), 263 (20), 152 (35), 108 (35).

(2,6-Diiodo-3,4,5-trimethoxy-phenyl)-methanol (394).



393
$C_{10}H_{14}O_4$
(198.22)

394
$C_{10}H_{12}I_2O_4$
(450.01)

To a solution of 3,4,5-trimethoxybenzyl alcohol (**393**) (1.01 mmol, 0.20 g) in chloroform (20 mL), at 0 ºC under nitrogen, was added silver trifluoroacetate (2.53 mmol, 0.56 g). To this suspension was added drop-wise a solution of iodine (2.53 mmol, 0.64 g) in chloroform (100 mL). After 16 h at room temperature the filtered and the filtrate washed with a saturated solution of sodium thiosulfate (100 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the benzyl alcohol (**394**) as a yellow oil (1.01 mmol, 0.45 g, 99%).

Novel

IR (ATR / golden gate): 3506 (w), 3387 (w), 2999 (w), 2929 (w), 2880 (w), 2840 (w), 1459 (m), 1438 (m), 1398 (m), 1370 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 5.06 (2H, s, C**H**$_2$OH), 3.83 (3H, s, OC**H**$_3$), 3.81 (6H, s, 2 x OC**H**$_3$), 2.40 (1H, b, s, O**H**).

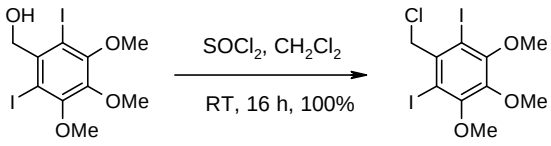
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 154.2 (2x**C**), 145.0 (**C**), 139.7 (**C**), 92.9 (2x**C**I), 75.0 (**C**H$_2$), 61.3 (O**C**H$_3$), 61.0 (2xO**C**H$_3$).

EIMS: *m/z* (%): 450 $[M]^{+\cdot}$ (100), 433 (20), 324 (15).

HRMS (ES +ve): $C_{10}H_{12}I_2NaO_4$ $[M+Na]^+$ 472.8723, found 472.8417.

1-Chloromethyl-2,6-diiodo-3,4,5-trimethoxy-benzene (395).



394
$C_{10}H_{12}I_2O_4$
(450.01)

395
$C_{10}H_{11}ClI_2O_3$
(468.46)

To a solution of benzyl alcohol (**394**) (0.89 mmol, 0.40 g) in DCM (40 mL), at 0 ºC under nitrogen, was added thionyl chloride (0.89 mmol, 0.07 mL) drop-wise. After 16 h at room temperature the reaction mixture was concentrated *in vacuo* to give benzyl chloride (**395**) as a yellow oil (0.89 mmol, 0.42 g, 100%).

Novel

IR (ATR / golden gate): 3003 (w), 2966 (w), 2933 (w), 2856 (w), 1456 (s), 1399 (s), 1371 (s), 1315 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 5.13 (2H, s, ClC**H**$_2$Ar), 3.92 (3H, s, OC**H**$_3$), 3.89 (6H, s, 2 x OC**H**$_3$).

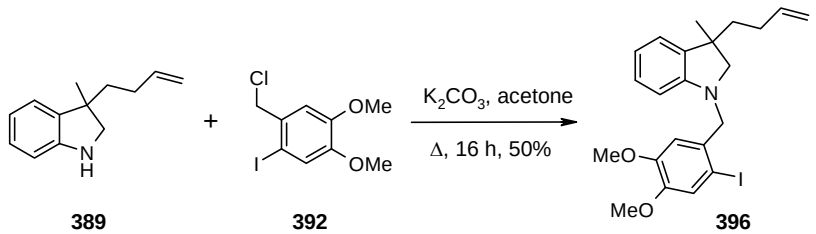
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 154.7 (2x**C**), 145.4 (**C**), 137.2 (**C**), 93.0 (2x**C**I), 61.4 (O**C**H$_3$), 61.1 (2xO**C**H$_3$), 58.2 (**C**H$_2$).

EIMS: *m/z* (%): 468 $[M]^{+\cdot}$ (90), 434 $[M-Cl]^{+\cdot}$ (100), 419 (10), 291 (20), 277 (15).

HRMS (EI): $C_{10}H_{11}ClI_2O_3$ $[M]^+$ 467.8486, found 467.8494.

3-But-3-enyl-1-(2-iodo-4,5-dimethoxy-benzyl)-3-methyl-2,3-dihydro-1*H*-indole (396).



389
$C_{13}H_{17}N$
(187.29)

392
$C_9H_{10}ClIO_2$
(312.54)

396
$C_{22}H_{26}INO_2$
(463.36)

A solution of indoline (**389**) (0.32 mmol, 60 mg), benzyl chloride (**392**) (0.27 mmol, 83 mg) and K_2CO_3 (1.67 mmol, 0.23 g) in acetone (20 mL) under nitrogen was heated at reflux for 16 h then cooled and concentrated *in vacuo*. The residue was partitioned between water (50 mL) and ether (50 mL). The aqueous phase was washed with ether (2 x 30 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 5% diethyl ether in petroleum ether) to give the desired product (**396**) as a yellow oil (0.14 mmol, 63 mg, 50%).

Novel

IR (ATR / golden gate): 3387 (b, w), 2958 (w), 2929 (w), 2827 (w), 1716 (w), 1638 (w), 1605 (m), 1498 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.29 (1H, s, aromatic C**H**), 7.09 (1H, app. td, *J*=7.7, 1.2 Hz, aromatic C**H**), 7.04 (1H, dd, *J*=7.4, 1.2 Hz, aromatic C**H**), 6.97 (1H, s, aromatic C**H**), 6.74 (1H, app. td, *J*=7.4, 0.9 Hz, aromatic C**H**), 6.48 (1H, d, *J*=7.7 Hz, aromatic C**H**), 5.79 (1H, ddt, *J*=16.9, 10.3, 6.6 Hz, C**H**=CH_2), 5.03–4.88 (2H, m, CH=C**H**$_2$), 4.26 (1H, d, *J*=15.4 Hz, NC**H**HAr), 4.13 (1H, d, *J*=15.4 Hz, NCH**H**Ar), 3.89 (3H, s, OC**H**$_3$), 3.78 (3H, s, OC**H**$_3$), 3.30 (1H, d, *J*=8.8 Hz, NC**H**H), 3.10 (1H, d, *J*=8.8 Hz, NCH**H**), 2.17 (1H, m, CH_2C**H**HCH=CH_2), 1.95 (1H, m, CH_2CH**H**CH=CH_2), 1.82–1.64 (2H, m, C**H**$_2$$CH_2$CH=$CH_2$), 1.35 (3H, s, C**H**$_3$).

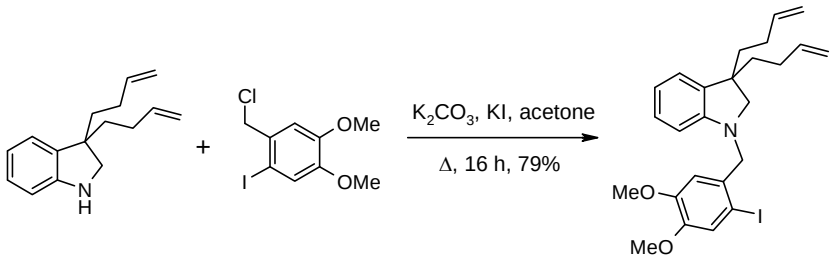
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 151.5 (**C**), 149.9 (**C**), 149.0 (**C**), 139.2 (**C**H), 137.5 (**C**), 133.0 (**C**), 127.9 (**C**H), 122.7 (**C**H), 122.1 (**C**H), 118.2 (**C**H), 114.5 (**C**H_2), 112.1 (**C**H), 107.3 (**C**H), 86.6 (**C**I), 66.2 (**C**H_2), 58.1 (**C**H_2), 56.6 (O**C**H_3), 56.2 (O**C**H_3), 43.9 (**C**), 40.5 (**C**H_2), 29.6 (**C**H_2), 26.3 (**C**H_3).

ESMS: *m/z* (%): 464 $[M+H]^+$ (100), 486 $[M+Na]^+$ (20).

HRMS (ES +ve): $C_{22}H_{26}INO_2$ $[M+H]^+$ 464.1081, found 464.1085.

3,3-Di-but-3-enyl-1-(2-iodo-4,5-dimethoxy-benzyl)-2,3-dihydro-1*H*-indole (397).



386
$C_{16}H_{21}N$
(227.35)

392
$C_9H_{10}ClIO_2$
(312.54)

397
$C_{25}H_{30}INO_2$
(503.43)

A solution of indoline (**386**) (1.32 mmol, 0.30 g), benzyl chloride (**392**) (1.98 mmol, 0.62 g), K_2CO_3 (8.18 mmol, 1.13 g) and KI (1.98 mmol, 0.33 g) in acetone (30 mL) under nitrogen was heated at reflux for 16 h then cooled and concentrated *in vacuo*. The residue was partitioned between water (30 mL) and ether (30 mL). The aqueous phase was washed with ether (2 x 30 mL) then the combined organic phases were washed with brine (80 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 5% diethyl ether in petroleum ether) to give the desired product (**397**) as a yellow oil (1.04 mmol, 0.53 g, 79%).

Novel

IR (ATR / golden gate): 3072 (w), 2995 (w), 2929 (w), 2905 (w), 2884 (w), 1638 (w), 1603 (m), 1497 (s), 1459 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.30 (1H, s, aromatic C**H**), 7.09 (1H, app. td, *J*=7.7, 1.1 Hz, aromatic C**H**), 7.01 (1H, dd, *J*=7.3, 0.7 Hz, aromatic C**H**), 6.95 (1H, s, aromatic C**H**), 6.73 (1H, app. td, *J*=7.3, 1.1 Hz, aromatic C**H**), 6.45 (1H, d, *J*=7.7 Hz, aromatic C**H**), 5.80 (2H, ddt, *J*=17.0, 10.4, 6.3 Hz, 2 x C**H**=CH_2), 5.04–4.88 (4H, m, 2 x CH=C**H**$_2$), 4.21 (2H, s, NC**H**$_2$Ar), 3.89 (3H, s, OC**H**$_3$), 3.76 (3H, s, OC**H**$_3$), 3.26 (2H, s, NC**H**$_2$), 2.23–2.06 (2H, m, 2 x C**H**H), 2.02–1.88 (2H, m, 2 x C**H**H), 1.87–1.64 (4H, m, 4 x CH**H**).

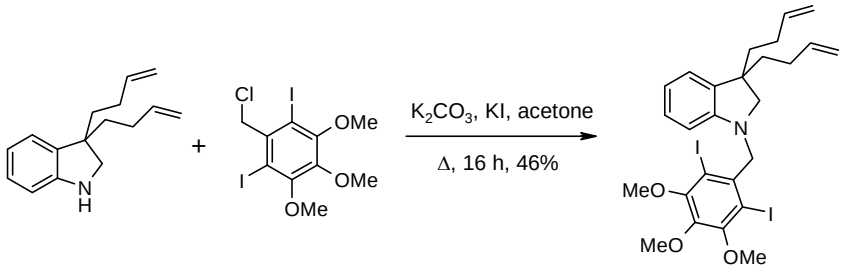
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 151.7 (**C**), 149.6 (**C**), 148.6 (**C**), 138.7 (2x**C**H), 135.0 (**C**), 132.6 (**C**), 127.7 (**C**H), 123.0 (**C**H), 121.7 (**C**H), 117.7 (**C**H), 114.3 (2x**C**H_2), 111.6 (**C**H), 106.8 (**C**H), 86.1 (**C**I), 63.8 (**C**H_2), 57.9 (**C**H_2), 56.2 (O**C**H_3), 55.8 (O**C**H_3), 47.0 (**C**), 38.5 (2x**C**H_2), 28.9 (2x**C**H_2).

ESMS: *m/z* (%): 504 $[M+H]^+$ (100), 526 $[M+Na]^+$ (25).

HRMS (ES +ve): $C_{25}H_{31}INO_2$ $[M+H]^+$ 504.1399 found 504.1394.

3,3-Di-but-3-enyl-1-(2,6-diiodo-3,4,5-trimethoxy-benzyl)-2,3-dihydro-1*H*-indole (398).



386
$C_{16}H_{21}N$
(227.35)

395
$C_{10}H_{11}ClI_2O_3$
(468.46)

398
$C_{26}H_{31}I_2NO_3$
(659.35)

A solution of indoline (**386**) (1.76 mmol, 0.40 g), benzyl chloride (**395**) (1.47 mmol, 0.69 g), K_2CO_3 (9.11 mmol, 1.26 g) and KI (1.47 mmol, 0.24 g) in acetone (50 mL) under nitrogen was heated at reflux for 16 h then cooled and concentrated *in vacuo*. The residue was partitioned between water (40 mL) and ether (40 mL). The aqueous phase was washed with ether (2 x 40 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 2% diethyl ether in petroleum ether) to give the desired product (**398**) (0.67 mmol, 0.44 g, 46%) as a light brown solid.

Novel

Mpt: °C 79–81 °C (EtOAc in hexanes).

IR (ATR / golden gate): 3064 (w), 3007 (w), 2962 (w), 2933 (w), 2909 (w), 2852 (w), 1634 (w), 1603 (m), 1491 (s), 1456 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.15 (1H, app. td, *J*=7.7, 1.1 Hz, aromatic C**H**), 6.98 (1H, dd, *J*=7.3, 1.1 Hz, aromatic C**H**), 6.75–6.67 (2H, m, 2 x aromatic C**H**), 5.76 (2H, ddt, *J*=16.9, 10.3, 6.4 Hz, 2 x C**H**=CH_2), 5.00–4.85 (4H, m, 2 x CH=C**H**$_2$), 4.71 (2H, s, NC**H**$_2$Ar), 3.96 (3H, s, OC**H**$_3$), 3.92 (6H, s, 2 x OC**H**$_3$), 3.07 (2H, s, NC**H**$_2$), 2.13–1.97 (2H, m, 2 x C**H**H), 1.95–1.80 (2H, m, 2 x C**H**H), 1.79–1.57 (4H, m, 4 x CH**H**).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

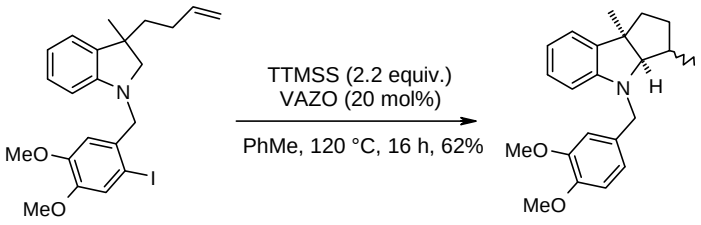
δ ppm 154.2 (2x**C**), 151.4 (**C**), 144.8 (**C**), 139.4 (2x**C**H), 136.8 (**C**), 135.7 (**C**), 127.8 (**C**H), 123.3 (**C**H), 117.8 (**C**H), 114.4 (2x**C**H_2), 107.5 (**C**H), 94.3 (2x**C**I), 62.0 (2x**C**H_2), 61.4 (O**C**H_3), 61.1 (2xO**C**H_3), 47.1 (**C**), 38.5 (2x**C**H_2), 29.3 (2x**C**H_2).

ESMS: *m/z* (%): 660 $[M+H]^+$ (100), 682 $[M+Na]^+$ (10).

HRMS (ES +ve): $C_{26}H_{32}I_2NO_3$ $[M+H]^+$ 660.0472, found 660.0466.

CHN: Calcd for $C_{26}H_{31}I_2NO_3$: C, 47.36, H, 4.74, N, 2.12. Found: C, 47.46, H, 4.73, N, 2.02.

4-(3,4-Dimethoxy-benzyl)-3,8b-dimethyl-1,2,3,3a,4,8b-hexahydro-cyclopenta[*b*]indole (399).



396
$C_{22}H_{26}INO_2$
(463.36)

399
$C_{22}H_{27}NO_2$
(337.47)

To a solution of **396** (0.13 mmol, 60 mg) in toluene (20 mL) under nitrogen was added TTMSS (0.29 mmol, 88 μL) and VAZO (0.03 mmol, 6 mg). The reaction mixture was heated at reflux and stirred for 16 h, then cooled, concentrated *in vacuo* and purified by column chromatography (silica, 50% $CHCl_3$ in petroleum ether) to give, contaminated with ~10% silicon residues that we were unable to remove, the desired product (**399**) as a brown oil (0.08 mmol, 27 mg, 62%).

Novel

IR (ATR / golden gate): 2945 (w), 2930 (w), 2892 (w), 2854 (w), 1697 (w), 1599 (w), 1512 (w).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.02–6.94 (2H, m, 2 x aromatic C**H**), 6.82–6.76 (3H, m, 3 x aromatic C**H**), 6.65 (1H, app. td, *J*=7.3, 0.9 Hz, aromatic C**H**), 6.32 (1H, d, *J*=7.8 Hz, aromatic C**H**), 4.52 (1H, d, *J*=16.2 Hz, NC**H**HAr), 4.19 (1H, d, *J*=16.2 Hz, NCH**H**Ar), 3.86 (3H, s, OC**H**$_3$), 3.78 (3H, s, OC**H**$_3$), 3.53 (1H, d, *J*=5.5 Hz, NC**H**), 2.17–1.84 (3H, m, NCHC**H**(CH_3)C**H**$_2$$CH_2$), 1.73–1.57 (2H, m, NCHCH(CH_3)CH_2C**H**$_2$), 1.36 (3H, s, CC**H**$_3$), 1.08 (3H, d, *J*=6.9 Hz, NCHCH(C**H**$_3$)CH_2CH_2).

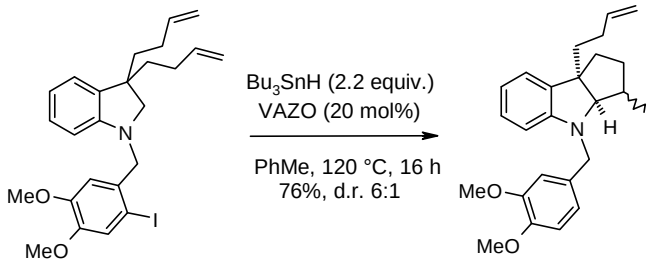
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 153.2 (**C**), 149.2 (**C**), 148.0 (**C**), 138.8 (**C**), 131.9 (**C**), 127.5 (**C**H), 122.5 (**C**H), 119.4 (**C**H), 117.6

(**C**H), 111.3 (**C**H), 110.6 (**C**H), 107.4 (**C**H), 79.4 (N**C**H), 56.1 (O**C**H_3), 55.9 (O**C**H_3), 53.9 (**C**H_2), 53.2 (**C**), 42.4 (**C**H_2), 41.5 (**C**H), 33.6 (**C**H_2), 29.3 (**C**H_3), 15.1 (**C**H_3).

^{1}H-^{1}H correlation obtained to confirm above NMR assignments.

8b-But-3-enyl-4-(3,4-dimethoxy-benzyl)-3-methyl-1,2,3,3a,4,8b-hexahydro-cyclopenta[*b*]indole (400).



397
$C_{25}H_{30}INO_2$
(503.43)

400
$C_{25}H_{31}NO_2$
(377.53)

To a solution of **397** (0.40 mmol, 0.20 g) in anhydrous toluene (20 mL) under nitrogen was added tributyltin hydride (0.87 mmol, 0.24 mL) and VAZO (0.08 mmol, 20 mg). The reaction mixture was heated at reflux for 4 h then cooled and concentrated *in vacuo* and purified by column chromatography (10% anhydrous K_2CO_3: 90% silica, 10% diethyl ether in petroleum ether) to give the desired product (**400**) as a brown oil (0.31 mmol, 0.12 g, 76%), as a 6:1 mixture of diastereoisomers.

Novel

IR (ATR / golden gate): 3077 (w), 3003 (w), 2929 (m), 2856 (m), 2827 (m), 1601 (s), 1513 (s), 1485 (s), 1461 (s).

^{1}H NMR (400 MHz, CHLOROFORM-*d*) (Major diastereoisomer reported)

δ ppm 7.48 (1H, app. td, *J*=7.9, 1.1 Hz, aromatic C**H**), 7.43 (1H, dd, *J*=7.3, 1.1 Hz, aromatic C**H**), 7.34–7.28 (3H, m, 3 x aromatic C**H**), 7.13 (1H, app. td, *J*=7.3, 0.6 Hz, aromatic C**H**), 6.87 (1H, d, *J*=7.9 Hz, aromatic C**H**), 6.16 (1H, ddt, *J*=16.7, 10.7, 6.1 Hz, CH_2=C**H**), 5.39–5.31 (2H, m, C**H**$_2$=CH), 5.04 (1H, d, *J*=15.9 Hz, NC**H**HAr), 4.65 (1H, d, *J*=15.9 Hz, NC**H**HAr), 4.34 (3H, s, OC**H**$_3$), 4.25 (3H, s, OC**H**$_3$), 4.11 (1H, d, *J*=5.8 Hz, NC**H**), 2.59–2.46 (2H, m, CH_2=CHC**H**$_2$CH$_2$), 2.45–2.35 (2H, m, CH_2=CHCH$_2$C**H**$_2$), 2.34–2.02 (4H, m, CH_3CHC**H**$_2$C**H**$_2$C), 1.82 (1H, m,

$CH_3C\mathbf{H}CH_2CH_2C$), 1.57 (3H, d, *J*=6.9 Hz, $C\mathbf{H}_3CHCH_2CH_2C$).

^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*)

(Major diastereoisomer reported)

δ ppm 153.2 (**C**), 148.9 (**C**), 148.0 (**C**), 138.8 (**C**H), 136.3 (**C**), 131.2 (**C**), 127.3 (**C**H), 122.8 (**C**H), 119.8 (**C**H), 117.1 (**C**H), 113.9 ($\mathbf{C}H_2$), 111.0 (**C**H) 110.9 (**C**H), 107.0 (**C**H), 75.0 (**C**H), 56.9 (**C**), 55.8 ($O\mathbf{C}H_3$), 55.7 ($O\mathbf{C}H_3$), 53.3 ($\mathbf{C}H_2$), 41.5 (**C**H), 40.9 ($\mathbf{C}H_2$), 40.6 ($\mathbf{C}H_2$), 32.6 ($\mathbf{C}H_2$), 30.1 ($\mathbf{C}H_2$), 14.9 ($\mathbf{C}H_3$).

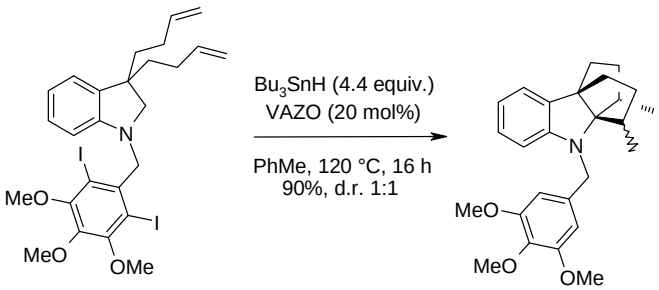
N.B. Additional signals attributed to the minor diastereoisomer.

^{1}H-^{1}H correlation obtained to confirm above NMR assignments.

CIMS: *m/z* (%): 378 $[M+H]^+$ (30), 151 $[M\text{-}CH_2C_6H_3(OCH_3)_2]^+$ (100).

HRMS (EI): $C_{25}H_{31}NO_2$ $[M]^+$ 378.2434, found 378.5428.

2-Aza-2-benzyl-8,11-dimethyl benz[c]tricycle[3,3,3,0^{1,5}]undecane (401).



398
$C_{26}H_{31}I_2NO_3$
(659.35)

401
$C_{26}H_{33}NO_3$
(407.56)

To a solution of **398** (0.46 mmol, 0.30 g) in toluene (20 mL) under nitrogen was added tributyltin hydride (2.02 mmol, 0.55 mL) and VAZO (0.09 mmol, 23 mg). The reaction mixture was heated at reflux and stirred for 16 h, then cooled, concentrated *in vacuo* and purified by column chromatography (10% anhydrous K_2CO_3: 90% silica, 5-10% diethyl ether in petroleum ether) to give the desired product (**401**) as a white solid (0.41 mmol, 0.17 g, 90%), as a 1:1 mixture of diastereoisomers.

Novel

IR (ATR / golden gate): 2933 (m), 2868 (w), 2848 (w), 1687 (m), 1588 (m), 1499(m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*):

δ ppm 7.04 (1H, dd, *J*=7.3, 1.0 Hz, aromatic C**H**), 7.05 (1H, dd, *J*=7.3, 1.0 Hz, aromatic C**H**), 6.92 (1H, app. td, *J*=7.7, 1.4 Hz, aromatic C**H**), 6.91 (1H, app. td, *J*=7.7, 1.4 Hz, aromatic C**H**), 6.63 (1H+1H, app. tt, *J*=7.3, 1.0 Hz, aromatic C**H**), 6.57 (1H+1H, b s, aromatic C**H**), 6.53 (1H+1H, b s, aromatic C**H**), 6.01 (1H, d, *J*=7.6 Hz, aromatic C**H**), 5.95 (1H, d, *J*=7.6 Hz, aromatic C**H**), 4.72 (1H, d, *J*=16.8 Hz, NC**H**HAr), 4.44 (1H+1H, s, NCH**H**Ar), 4.25 (1H, d, *J*=16.8 Hz, NC**H**HAr), 3.868 (3H, s, OC**H**$_3$), 3.864 (3H, s, OC**H**$_3$), 3.788 (6H, s, 2 x OC**H**$_3$), 3.786 (6H, s, 2 x OC**H**$_3$), 2.19–1.97 (4H+4H, m, 2 x 2 x C**H** and C**H**H), 1.94–1.76 (2H+2H, m, 2 x 2 x C**H**H), 1.75–1.57 (2H+2H,

m, 2 x 2 x CH**H**), 1.54–1.32 (2H+2H, m, 2 x 2 x CH**H**), 1.26 (3H, d, *J*=6.9 Hz, CHC**H**$_3$), 1.11 (3H, d, *J*=6.9 Hz, CHC**H**$_3$), 0.92 (3H+3H, d, *J*=7.0 Hz, 2 x CHC**H**$_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*):

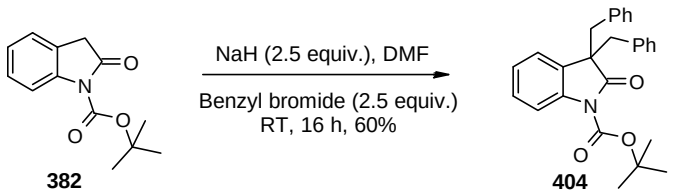
δ ppm 153.4 (2x**C**), 152.6+151.8 (**C**), 138.5+137.9 (**C**), 135.3 (**C**), 135.1 (**C**), 127.2+127.2 (**C**H), 122.7+122.5 (**C**H), 117.3+117.0 (**C**H), 107.5 (**C**H), 105.7 (**C**H), 103.8+103.7 (**C**H), 91.4+87.4 (**C**), 67.5+64.3 (**C**), 61.1 (O**C**H$_3$), 56.3+56.2 (2xO**C**H$_3$), 52.8+50.8 (**C**H$_2$), 44.0+43.6 (2x**C**H), 41.5+41.1+40.1 (2x**C**H$_2$), 35.0+34.3+33.8 (2x**C**H$_2$), 16.4+15.2+15.1 (2x**C**H$_3$).

^{1}H-^{1}H and ^{1}H-^{13}C correlations obtained to confirm above NMR assignments.

ESMS: *m/z* (%): 408 $[M+H]^+$ (50), 228 $[M-CH_2Ar+H]^+$ (100).

HRMS (ES +ve): $C_{26}H_{33}NNaO_3$ $[M+Na]^+$ 430.2358, found 430.2353.

***tert*-Butyl 3,3-dibenzyl-2-oxo-2,3-dihydro-indole-1-carboxylate (404).**



382
$C_{13}H_{15}NO_3$
(233.27)

404
$C_{27}H_{27}NO_3$
(413.52)

To a solution of Boc-oxindole (**382**) (6.35 mmol, 1.48 g) in anhydrous DMF (100 mL) at 0 ºC under nitrogen was added sodium hydride (60% in mineral oil, 15.86 mmol, 0.64 g). After 2 h at 0 ºC benzyl bromide (19.05 mmol, 2.27 mL) was added followed after 16 h by water (100 mL). The reaction mixture was extracted with ether (2 x 100 mL), then the combined organic phases were washed with water (3 x 200 mL), brine (200 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 5-10% diethyl ether in petroleum ether) to give **404** as a yellow oil (3.62 mmol, 1.50 g, 57%).

Novel

IR (ATR / golden gate): 3085(w), 3064 (w), 3032 (w), 2987 (w), 2913 (w), 1785 (m), 1762 (s), 1728 (s).

^{1}H NMR (400 MHz, CHLOROFORM-*d*)

δ ppm 7.39 (1H, m, aromatic C**H**), 7.20 (1H, m, aromatic C**H**), 7.16–7.10 (3H, m, 3 x aromatic C**H**), 7.10–7.03 (5H, m, 5 x aromatic C**H**), 6.93 - 6.86 (4H, m, 4 x aromatic C**H**), 3.38 (2H, d, *J*=13.1 Hz, 2 x C**H**HAr), 3.18 (2H, d, *J*=13.1 Hz, 2 x CH**H**Ar), 1.51 (9H, s, C(C**H**$_3$)$_3$).

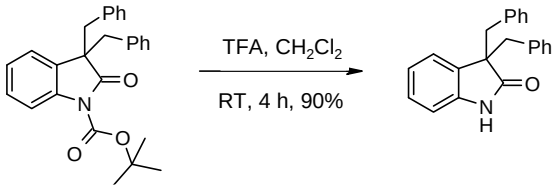
^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*)

δ ppm 177.5 (**C**=O), 148.5 (**C**=O), 139.8 (**C**), 135.4 (2x**C**), 130.0 (4x**C**H), 129.0 (**C**), 128.0 (**C**H), 127.7 (4x**C**H), 126.6 (2x**C**H), 124.1 (**C**H), 123.5 (**C**H), 114.6 (**C**H), 83.6 (**C**), 56.4 (**C**), 44.3 (2x**C**H$_2$), 28.0 (3x**C**H$_3$).

ESMS: *m/z* (%): 436 $[M+Na]^+$ (50), 849 $[M_2+Na]^+$ (100).

HRMS (ES +ve): $C_{27}H_{27}NNaO_3$ $[M+Na]^+$ 436.1889, found 436.1883.

3,3-Dibenzyl-1,3-dihydro-indol-2-one (405).



404
$C_{27}H_{27}NO_3$
(413.52)

405
$C_{22}H_{19}NO$
(313.40)

To a solution of *N*-Boc oxindole (**404**) (3.62 mmol, 1.50 g) in dichloromethane (200 mL) under nitrogen at 0 ºC was added TFA (10 mL). After 4 h at room temperature the reaction mixture was concentrated *in vacuo* to give oxindole (**405**) as a white solid (3.26 mmol, 1.02 g, 90%). Data consistent with the literature.[81]

IR (ATR / golden gate): 3142 (w), 3077 (w), 2023 (w), 2938 (w), 2913 (w), 2880 (w), 2856 (w), 2823 (w), 1713 (s), 1667 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

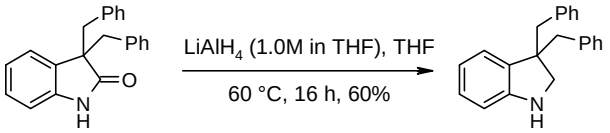
δ ppm 8.62 (1H, b s, N**H**), 7.28 (1H, m, aromatic C**H**), 7.19–7.02 (8H, m, 8 x aromatic C**H**), 6.98–6.87 (4H, m, 4 x aromatic C**H**), 6.56 (1H, m, aromatic C**H**), 3.37 (2H, d, *J*=13.2 Hz, 2 x C**H**HPh), 3.27 (2H, d, *J*=13.2 Hz, 2 x CH**H**Ph).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 183.4 (**C**=O), 139.8 (**C**), 135.1 (2x**C**), 130.7 (**C**), 129.9 (4x**C**H), 128.2 (**C**H), 127.8 (4x**C**H), 126.8 (2x**C**H), 124.6 (**C**H), 122.8 (**C**H), 110.4 (**C**H), 57.6 (**C**), 43.3 (2x**C**H_2).

CIMS: *m/z* (%): 313 $[M+H]^{+\cdot}$ (100), 222 $[M-CH_2Ph]^{+\cdot}$ (100), 204 (35), 91 (75).

3,3-Dibenzyl-2,3-dihydro-1*H*-indole (406).



405
$C_{22}H_{19}NO$
(313.40)

406
$C_{22}H_{21}N$
(299.42)

A solution of $LiAlH_4$ (1.0 M solution in THF, 9.78 mmol, 9.78 mL) was diluted with anhydrous THF (100 mL) and cooled to 0 ºC under nitrogen. A solution of oxindole (**405**) (3.26 mmol, 1.02 g) in anhydrous THF (20 mL) was added drop-wise and the reaction mixture then heated to 70 ºC for 16 h then cooled to 0 ºC. Water (200 mL) was then added cautiously, then the reaction mixture was extracted with ether (3 x 70 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 20% diethyl ether in petroleum ether) to give indoline (**406**) as a brown oil (1.91 mmol, 0.57 g, 60%).

Novel

IR (ATR / golden gate): 3386 (m), 3081(w), 3052 (w), 3019 (w), 2917 (w), 2852 (w), 1605 (m), 1487 (s), 1462 (m), 1453 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.24–7.17 (6H, m, 6 x aromatic C**H**), 7.09–6.94 (6H, m, 6 x aromatic C**H**), 6.77 (1H, app. td, *J*=7.3, 0.9 Hz, aromatic C**H**), 6.53 (1H, d, *J*=7.8 Hz, aromatic C**H**), 3.43 (2H, s, NHC$\mathbf{H}_2$), 3.10 (2H, d, *J*=13.4 Hz, 2 x C**H**HAr), 3.00 (2H, d, *J*=13.5 Hz, 2 x CH**H**Ar).

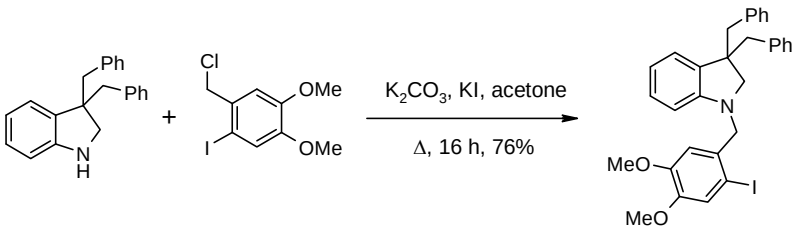
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 151.7 (**C**), 138.6 (2x**C**), 134.6 (**C**), 131.0 (4x**C**H), 128.1 (4x**C**H), 126.5 (3x**C**H), 124.6 (**C**H), 118.7 (**C**H), 110.5 (**C**H), 55.6 (**C**H_2), 51.5 (**C**), 45.1 (2x**C**H_2).

ESMS: *m/z* (%): 300 $[M+H]^+$ (100).

HRMS (ES +ve): $C_{22}H_{21}N$ $[M+H]^+$ 300.1752, found 300.1747.

3,3-Dibenzyl-1-(2-iodo-4,5-dimethoxy-benzyl)-2,3-dihydro-1*H*-indole (407).



406
$C_{22}H_{21}N$
(299.42)

392
$C_9H_{10}ClIO_2$
(312.54)

407
$C_{31}H_{30}INO_2$
(575.49)

A solution of indoline (**406**) (0.84 mmol, 0.25 g), benzyl chloride (**392**) (1.25 mmol, 0.39 g), K_2CO_3 (5.04 mmol, 0.70 g) and KI (1.25 mmol, 0.21 g) in acetone (60 mL) under nitrogen was heated at reflux for 16 h the cooled and concentrated *in vacuo*. The residue was partitioned between water (50 mL) and ether (50 mL). The aqueous phase was washed with ether (2 x 50 mL) then the combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 5% diethyl ether in petroleum ether) to give the desired product (**407**) as a brown oil (0.64 mmol, 0.37 g, 76%).

Novel

IR (ATR / golden gate): 3064 (w), 3023 (w), 2999 (w), 2909 (w), 2848 (w), 1711 (s), 1601 (m), 1496 (s).

^{1}H NMR (400 MHz, CHLOROFORM-*d*)

δ ppm 7.24 (1H, s, aromatic C**H**), 7.23–7.16 (6H, m, 6 x aromatic C**H**), 7.08 (1H, app. td, *J*=7.6, 1.2 Hz, aromatic C**H**), 7.00–6.95 (4H, m, 4 x aromatic C**H**), 6.91 (1H, dd, *J*=7.3, 0.9 Hz, aromatic C**H**), 6.71 (1H, app. t, *J*=7.4 Hz, aromatic C**H**), 6.69 (1H, s, aromatic C**H**), 6.37 (1H, d, *J*=7.8 Hz, aromatic C**H**), 3.98 (2H, s, NC**H**$_2$Ar), 3.87 (3H, s, OC**H**$_3$), 3.65 (3H, s, OC**H**$_3$), 3.27 (2H, s, NC**H**$_2$), 3.09 (2H, d, *J*=13.4 Hz, 2 x C**H**HAr), 2.98 (2H, d, *J*=13.6 Hz, 2 x CH**H**Ar).

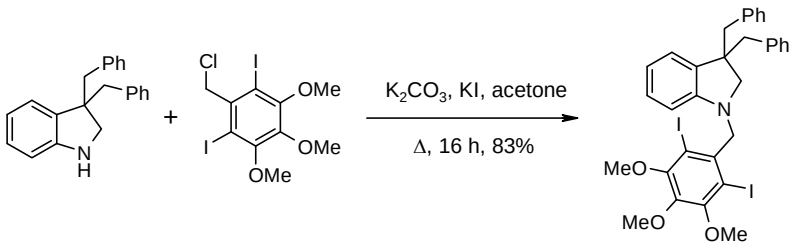
^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*)

δ ppm 151.6 (**C**), 149.5 (**C**), 148.6 (**C**), 138.0 (2x**C**), 134.3 (**C**), 132.6 (**C**), 130.7 (4x**C**H), 127.9 (**C**H), 127.8 (4x**C**H), 126.2 (2x**C**H), 124.2 (**C**H), 121.7 (**C**H), 117.3 (**C**H), 112.1 (**C**H), 107.3 (**C**H), 86.4 (**C**I), 61.8 (**C**H_2), 57.8 (**C**H_2), 56.2 (O**C**H_3), 56.0 (O**C**H_3), 49.9 (**C**), 44.3 (2x**C**H_2)

ESMS: *m/z* (%): 576 $[M+H]^+$ (100), 598 $[M+Na]^+$ (30).

HRMS (ES +ve): $C_{31}H_{30}INO_2$ $[M+H]^+$ 576.1399, found 576.1394.

3,3-Dibenzyl-1-(2,6-diiodo-3,4,5-trimethoxy-benzyl)-2,3-dihydro-1*H*-indole (408)



406
$C_{22}H_{21}N$
(299.42)

395
$C_{10}H_{11}ClI_2O_3$
(468.46)

408
$C_{32}H_{31}I_2NO_3$
(731.42)

A solution of indoline (**406**) (0.84 mmol, 0.25 g), benzyl chloride (**395**) (1.25 mmol, 0.59 g), K_2CO_3 (5.04 mmol, 0.70 g) and KI (1.25 mmol, 0.21 g) in acetone (60 mL) under nitrogen was heated at reflux for 16 h then cooled and concentrated *in vacuo*. The residue was partitioned between water (50 mL) and ether (50 mL). The aqueous phase was washed with ether (2 x 50 mL) then the combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 5% diethyl ether in petroleum ether) to give the desired product (**408**) (0.70 mmol, 0.51 g, 83%) as a cream solid.

Novel

Mpt: °C 96–99 °C (EtOAc in hexanes).

IR (ATR / golden gate): 3027 (w), 3003 (w), 2925 (w), 2848 (w), 1602 (m), 1487 (m), 1455 (s).

^{1}H NMR (400 MHz, CHLOROFORM-*d*):

δ ppm 7.20–7.10 (7H, m, 7 x aromatic C**H**), 6.95 (4H, app. dd, *J*=6.7, 2.9 Hz, 4 x aromatic C**H**), 6.85 (1H, dd, *J*=7.3, 0.6 Hz, aromatic C**H**), 6.69 (2H, app. dt, *J*=8.5, 7.3, 1.1 Hz, 2 x aromatic C**H**), 4.60 (2H, s, NC**H**$_2$Ar), 3.97 (3H, s, OC**H**$_3$), 3.91 (6H, s, 2 x OC**H**$_3$), 3.05 (2H, s, NC**H**$_2$), 2.98 (2H, d, *J*=13.5 Hz, 2 x C**H**HPh), 2.87 (2H, d, *J*=13.5 Hz, 2 x CH**H**Ph).

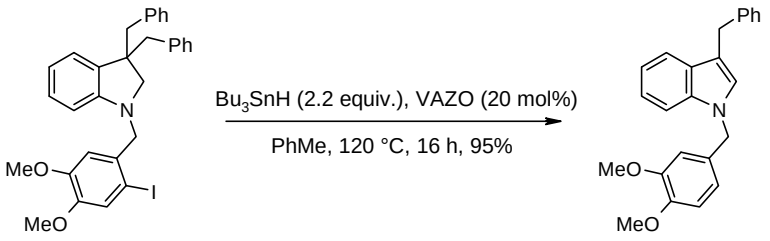
^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*):

δ ppm 154.0 (**C**), 150.8 (2x**C**), 144.6 (**C**), 138.4 (2x**C**), 136.8 (**C**), 134.9 (**C**), 131.1 (4x**C**H), 127.9 (4x**C**H), 127.7 (**C**H), 126.3 (2x**C**H), 124.2 (**C**H), 117.4 (**C**H), 107.6 (**C**H), 94.3 (2x**C**I), 61.6 (**C**H_2), 61.2 (O**C**H_3), 61.0 (2xO**C**H_3), 60.0 (**C**H_2), 49.8 (**C**), 43.2 (2x**C**H_2).

ESMS: *m/z* (%): 732 $[M+H]^+$ (100).

HRMS (ES +ve): $C_{32}H_{31}I_2NO_3$ $[M+H]^+$ 732.0472, found 732.0466.

3-Benzyl-1-(3,4-dimethoxy-benzyl)-1*H*-indole (410).



407
$C_{31}H_{30}INO_2$
(575.49)

410
$C_{24}H_{23}NO_2$
(357.46)

To a solution of **407** (0.61 mmol, 0.35 g) in toluene (25 mL) under nitrogen was added tributyltin hydride (1.34 mmol, 0.36 mL) and VAZO (0.12 mmol, 30 mg). The reaction mixture was heated at reflux for 16 h, cooled, concentrated *in vacuo* and purified by column chromatography (10% anhydrous K_2CO_3: 90% silica, 5% diethyl ether in petroleum ether) to give the desired product (**410**) (0.58 mmol, 0.21 g, 95%) as a brown oil.

Novel

IR (ATR / golden gate): 3052 (w), 3027 (w), 2999 (w), 2933 (w), 2901 (w), 2823 (w), 1514 (s), 1463 (m), 1452 (m).

^{1}H NMR (400 MHz, CHLOROFORM-*d*):

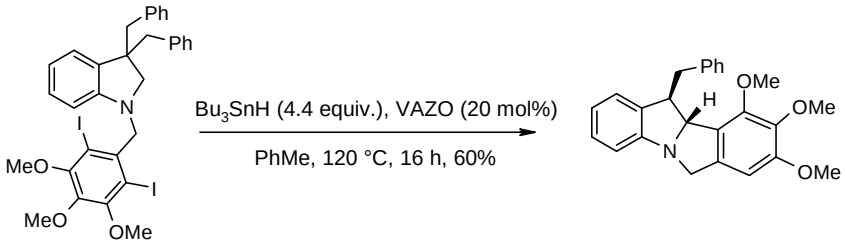
δ ppm 7.60 (1H, dd, *J*=7.8, 0.9 Hz, aromatic C**H**), 7.38–7.31 (4H, m, 4 x aromatic C**H**), 7.26–7.21 (3H, m, 3 x aromatic C**H**), 7.14 (1H, ddd, *J*=7.8, 6.9, 1.0 Hz, aromatic C**H**), 6.93 (1H, s, aromatic C**H**), 6.86 (1H, d, *J*=8.1 Hz, aromatic C**H**), 6.75 (1H, dd, *J*=8.1, 1.9 Hz, aromatic C**H**), 6.71 (1H, d, *J*=1.9 Hz, aromatic C**H**), 5.27 (2H, s, C$\mathbf{H}_2$Ar), 4.20 (2H, s, NC$\mathbf{H}_2$Ar), 3.92 (3H, s, OC$\mathbf{H}_3$), 3.83 (3H, s, OC$\mathbf{H}_3$).

^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*):

δ ppm 149.3 (**C**), 148.5 (**C**), 141.4 (**C**), 136.9 (**C**), 130.2 (2x**C**), 128.6 (2x**C**H), 128.3 (2x**C**H), 126.4 (**C**H), 125.8 (**C**H), 121.7 (**C**H), 119.3 (**C**H), 119.2 (**C**H), 119.0 (**C**H), 114.8 (**C**), 111.3 (**C**H), 110.1 (**C**H),

	109.6 (**C**H), 55.9 (O**C**H_3), 55.8 (O**C**H_3), 49.7 (**C**H_2), 31.5 (**C**H_2).
ESMS: *m/z* (%):	258 $[M+H]^+$ (100).
HRMS (ES +ve):	$C_{24}H_{24}NO_2$ $[M+H]^+$ 358.1807, found 358.1802.

11-Benzyl-8,9,10-trimethoxy-10b,11-dihydro-6*H*-isoindolo[2,1-*a*]indole (411).



408
$C_{32}H_{31}I_2NO_3$
(731.42)

411
$C_{25}H_{25}NO_3$
(387.48)

To a solution of **408** (0.68 mmol, 0.50 g) in toluene (40 mL) under nitrogen was added tributyltin hydride (3.01 mmol, 0.81 mL) and VAZO (0.14 mmol, 33 mg). The reaction mixture was heated at reflux for 16 h, cooled, concentrated *in vacuo* and purified by column chromatography (10% anhydrous K_2CO_3: 90% silica, 5% diethyl ether in petroleum ether) to give the desired product (**411**) (0.40 mmol, 0.16 g, 60%) as a colourless oil.

Novel

IR (ATR / golden gate): 3032 (w), 2995 (w), 2938 (w), 2856 (w), 1597 (w).

^{1}H NMR (400 MHz, CHLOROFORM-*d*):

δ ppm 7.42–7.36 (4H, m, 4 x aromatic C**H**), 7.31 (1H, m, aromatic C**H**), 7.17 (1H, app. dt, *J*=7.5, 1.3 Hz, aromatic C**H**), 6.87–6.80 (2H, m, 2 x aromatic C**H**), 6.78 (1H, ddd, *J*=7.9, 7.2, 0.8 Hz, aromatic C**H**), 6.51 (1H, s, aromatic C**H**), 5.06 (1H, b s, NC**H**), 4.55 (1H, dd, *J*=14.6, 1.3 Hz, NC**H**H), 4.48 (1H, d, *J*=14.6 Hz, NCH**H**), 4.18 (1H, b dt, *J*=7.5, 1.9 Hz, C**H**CH_2Ph), 3.83 (3H, s, OC**H**$_3$), 3.82 (3H, s, OC**H**$_3$), 3.70 (3H, s, OC**H**$_3$), 3.16 (1H, dd, *J*=13.3, 8.2 Hz, CHC**H**HPh), 3.07 (1H, dd, *J*=13.3, 7.3 Hz, CHCH**H**Ph).

^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*):

δ ppm 154.1 (**C**), 154.1 (**C**), 149.5 (**C**), 140.9 (**C**), 140.0 (**C**), 135.0 (**C**), 134.0 (**C**), 129.7 (2x**C**H), 128.2 (2x**C**H), 127.8 (**C**H), 127.1 (**C**), 126.1 (**C**H), 124.8

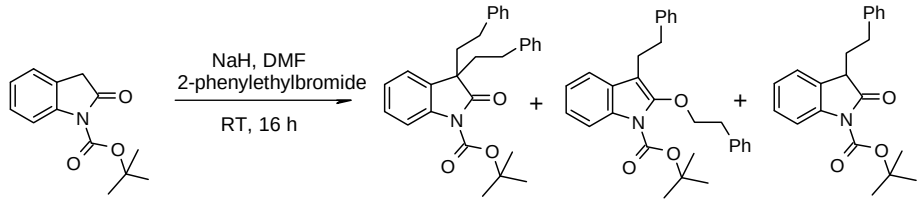
(**C**H), 120.3 (**C**H), 112.0 (**C**H), 101.3 (**C**H), 74.7 (**C**H), 60.8 (O**C**H_3), 60.3 (O**C**H_3), 59.4 (N**C**H_2), 56.1 (O**C**H_3), 48.1 (**C**H), 43.2 (**C**H_2).

^{1}H-^{1}H and ^{1}H-^{13}C correlations and NOESY experiment obtained to confirm above NMR assignments.

CIMS: *m/z* (%): 388 $[M+H]^{+\cdot}$ (80), 296 $[M-CH_2Ph]^{+\cdot}$ (100), 280 (15), 195 (20), 167 (20), 91 (30).

HRMS (ES +ve): $C_{25}H_{26}NO_3$ $[M+H]^+$ 388.1913, found 388.1907.

***tert*-Butyl 2-oxo-3,3-diphenethyl-2,3-dihydro-indole-1-carboxylate (419), *tert*-butyl 3-phenethyl-2-phenethyloxy-indole-1-carboxylate (439) and *tert*-butyl 2-oxo-3-phenethyl-2,3-dihydro-indole-1-carboxylate (440).**



382
$C_{13}H_{15}NO_3$
(233.27)

419, 42%
$C_{29}H_{31}NO_3$
(441.58)

439, 16%
$C_{29}H_{31}NO_3$
(441.58)

440, 11%
$C_{21}H_{23}NO_3$
(337.42)

To a solution of **382** (4.29 mmol, 1.00 g) in anhydrous DMF (100 mL) at 0 °C under argon, was added NaH (60% in mineral oil, 10.72 mmol, 0.43 g). After 1 h at 0 °C 2-phenylethylbromide (10.72 mmol, 1.5 mL) was added followed after 16 h at room temperature by water (100 mL). The reaction mixture was extracted ethyl acetate (3 x 100 mL) then the combined organic phases were washed with water (4 x 60 mL), brine (150 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 10% diethyl ether in petroleum ether) to give firstly *bis*-alkylated material **419** as a clear oil (1.79 mmol, 0.79 g, 42%), then *O*-alkylated material **439** as a clear oil (0.67 mmol, 0.29 g, 16%) and the *mono*-alkylated material **440** (0.48 mmol, 0.16 g, 11%) as a yellow oil.

Data for **419**

Novel

IR (ATR / golden gate): 3088 (w), 3054 (w), 3032 (w), 2979 (w), 2930 (w), 2858 (w), 1792 (m), 1763 (s), 1727 (s).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.89 (1H, d, *J*=8.1 Hz, aromatic C**H**), 7.37–7.09 (9H, m, 9 x aromatic C**H**), 7.06–6.98 (4H, m, 4 x aromatic C**H**), 2.47–2.27 (4H, m, 2 x $CH_2C\mathbf{H}_2Ph$), 2.25–1.98 (4H, m, 2 x $C\mathbf{H}_2CH_2Ph$), 1.67 (9H, s, $OC(C\mathbf{H}_3)_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 178.3 (**C**=O), 149.3 (**C**=O), 141.2 (2x**C**), 140.3 (**C**), 130.7 (**C**), 128.5 (8x**C**H), 126.2 (3x**C**H), 124.9 (**C**H), 122.8 (**C**H), 115.3 (**C**H), 84.5 (**C**), 53.4 (**C**), 40.9 (2x**C**H_2), 30.8 (2x**C**H_2), 28.3 (3x**C**H_3).

ESMS: *m/z* (%): 464 $[M+Na]^+$ (50), 906 $[M_2+Na]^+$ (100).

H**RMS (ES +ve)**: $C_{29}H_{31}NNaO_3$ $[M+Na]^+$ 464.2202, found 464.2196.

Data for **439**

Novel

IR (ATR / golden gate): 3066 (w), 3028 (w), 2979 (w), 2930 (w), 1726 (s), 1625 (m), 1591 (m), 1572 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.99 (1H, dd, *J*=6.8, 1.6 Hz, aromatic C**H**), 7.36 (1H, dd, *J*=6.6, 2.1 Hz, aromatic C**H**), 7.32–6.99 (12H, m, 12 x aromatic C**H**), 4.04 (2H, t, *J*=7.1 Hz, OC**H**$_2$CH$_2$Ph), 3.05 (2H, t, *J*=7.1 Hz, OCH$_2$C**H**$_2$Ph), 2.86–2.77 (2H, m, CH$_2$C**H**$_2$Ph), 2.76–2.67 (2H, m, C**H**$_2$CH$_2$Ph), 1.63 (9H, s, COOC(C**H**$_3$)$_3$).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 149.5 (**C**=O), 147.6 (**C**), 142.1 (**C**), 138.1 (**C**), 132.1 (**C**), 129.3 (2x**C**H), 128.6 (4x**C**H), 128.5 (2x**C**H), 128.1 (**C**), 126.7 (**C**H), 126.1 (**C**H), 123.4 (**C**H), 122.7 (**C**H), 118.4 (**C**H), 115.5 (**C**H), 105.2 (**C**), 83.7 (**C**), 76.9 (**C**H_2), 36.5 (**C**H_2), 35.9 (**C**H_2), 28.5 (3x**C**H_3), 25.1 (**C**H_2).

ESMS: *m/z* (%): 464 $[M+Na]^+$ (100), 906 $[M_2+Na]^+$ (20).

H**RMS (ES +ve)**: $C_{29}H_{31}NNaO_3$ $[M+Na]^+$ 464.2202, found 464.2196.

Data for **440**

Novel

IR (ATR / golden gate): 3085 (w), 3058 (w), 3028 (w), 2983 (w), 2933 (w), 2858 (w), 1792 (m), 1762 (m), 1727 (s), 1607 (w).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.86 (1H, d, *J*=8.1 Hz, aromatic C**H**), 7.39–7.15 (8H, m, 8 x aromatic C**H**), 3.61 (1H, t, *J*=5.9 Hz, C**H**CH_2CH_2Ph), 2.86–2.64 (2H, m, $CH_2C\mathbf{H}_2Ph$), 2.45–2.24 (2H, m, $C\mathbf{H}_2CH_2Ph$), 1.68 (9H, s, $COOC(C\mathbf{H}_3)_3$).

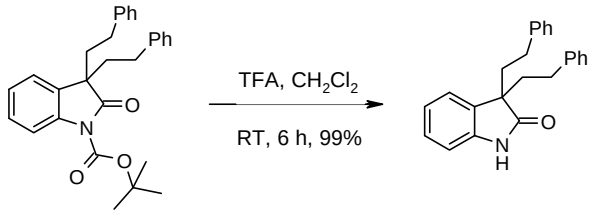
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 176.1 (**C**=O), 149.4 (**C**=O), 141.0 (**C**), 140.4 (**C**), 128.7 (2x**C**H), 128.6 (2x**C**H), 128.3 (**C**H), 127.9 (**C**), 126.3 (**C**H), 124.5 (**C**H), 123.7 (**C**H), 115.1 (**C**H), 84.4 (**C**), 45.4 (**C**H), 33.0 ($\mathbf{C}H_2$), 31.9 ($\mathbf{C}H_2$), 28.3 ($3x\mathbf{C}H_3$).

ESMS: *m/z* (%): 360 $[M+Na]^+$ (40), 697 $[M_2+Na]^+$ (100).

HRMS (ES +ve): $C_{21}H_{23}NNaO_3$ $[M+Na]^+$ 360.1576, found 360.1570.

3,3-Diphenethyl-1,3-dihydro-indol-2-one (420).



419
$C_{29}H_{31}NO_3$
(441.58)

420
$C_{24}H_{23}NO$
(341.46)

To a solution of oxindole **419** (1.77 mmol, 0.78 g) in dichloromethane (40 mL) under argon at 0 ºC was added TFA (2.0 mL). After 6 h at room temperature the reaction mixture was concentrated *in vacuo* to give the desired compound **420** as a brown oil (1.76 mmol, 0.60 g, 99%).

Novel

IR (ATR / golden gate): 3247 (w), 3081 (w), 3066 (w), 3032 (w), 2949 (w), 2915 (w), 2858 (w), 1777 (m), 1699 (m), 1620 (m), 1603 (m), 1471 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 9.80 (1H, b s, N**H**), 7.40–7.12 (9H, m, 9 x aromatic C**H**), 7.09–6.98 (5H, m, 5 x aromatic C**H**), 2.48–2.05 (8H, m, 2 x C**H**$_2$C**H**$_2$Ph).

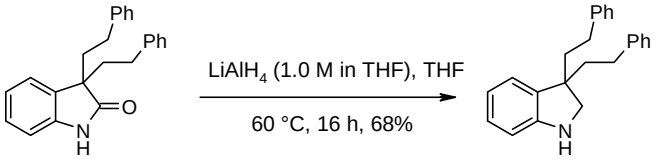
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 185.1 (**C**=O), 140.9 (2x**C**), 140.5 (**C**), 132.1 (**C**), 128.7 (**C**H), 128.5 (8x**C**H), 126.3 (2x**C**H), 124.2 (**C**H), 123.4 (**C**H), 111.1 (**C**H), 54.6 (**C**), 39.7 (2x**C**H$_2$), 30.7 (2x**C**H$_2$).

ESMS: *m/z* (%): 364 $[M+Na]^+$ (100).

HRMS (ES +ve): $C_{24}H_{24}NO$ $[M+H]^+$ 342.1858, found 342.1852.

3,3-Diphenethyl-2,3-dihydro-1*H*-indole (421).



420
$C_{24}H_{23}NO$
(341.46)

421
$C_{24}H_{25}N$
(327.47)

To a solution of **420** (2.34 mmol, 0.80 g) stirred in anhydrous THF (20 mL) at 0 °C under argon was added drop-wise $LiAlH_4$ (1.0 M solution in THF, 4.69 mmol, 4.7 mL). After 16 h at 60 ºC the reaction mixture was cooled to 0 ºC and water (50 mL) added cautiously. The reaction mixture was extracted with ether (3 x 50 mL), the organic phases combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **421** as a brown oil (1.58 mmol, 0.52 g, 68%).

Novel

IR (ATR / golden gate): 3387 (w), 3081 (w), 3058 (w), 3028 (w), 2922 (w), 2850 (w), 1599 (m), 1487 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.32–7.23 (4H, m, 4 x aromatic C**H**), 7.22–7.06 (8H, m, 8 x aromatic C**H**), 6.79 (1H, app. td, *J*=7.4, 0.6 Hz, aromatic C**H**), 6.69 (1H, d, *J*=7.6 Hz, aromatic C**H**), 3.55 (2H, s, NHC**H**$_2$), 2.70 (2H, app. td, *J*=12.8, 5.2 Hz, 2 x CH_2C**H**HPh), 2.51 (2H, app. td, *J*=12.8, 5.0 Hz, 2 x CH_2CH**H**Ph), 2.10 (2H, ddd, *J*=13.5, 12.3, 5.2 Hz, 2 x C**H**HCH_2Ph), 1.98 (2H, ddd, *J*=13.5, 12.5, 5.0 Hz, 2 x CH**H**CH_2Ph).

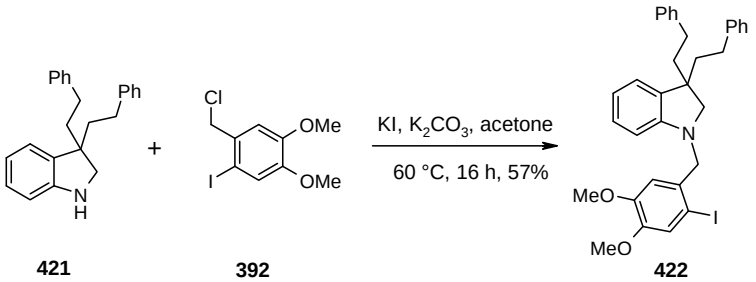
^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 151.5 (**C**), 142.8 (2x**C**), 134.8 (**C**), 128.5 (4x**C**H), 128.5 (4x**C**H), 127.9 (**C**H), 125.9 (2x**C**H), 123.5 (**C**H), 118.7 (**C**H), 109.8 (**C**H), 57.4 (**C**H_2), 49.2 (**C**), 41.4 (2x**C**H_2), 31.2 (2x**C**H_2).

ESMS: *m/z* (%): 328 $[M+H]^+$ (100).

HRMS (ES +ve): $C_{24}H_{26}N$ $[M+H]^+$ 328.2065, found 328.2060.

1-(2-Iodo-4,5-dimethoxy-benzyl)-3,3-diphenethyl-2,3-dihydro-1*H*-indole (422).



421
$C_{24}H_{25}N$
(327.47)

392
$C_9H_{10}ClIO_2$
(312.54)

422
$C_{33}H_{34}INO_2$
(603.55)

A solution of indoline **421** (0.93 mmol, 0.31 g), benzyl chloride **392** (1.12 mmol, 0.35 g), K_2CO_3 (5.58 mmol, 0.77 g) and KI (0.93 mmol, 0.15 g) in acetone (40 mL) under argon was heated at reflux for 16 h. The reaction mixture was cooled to room temperature and partitioned between water (50 mL) and ether (50 mL). The aqueous phase was extracted with ether (2 x 30 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 5→25% diethyl ether in petroleum ether) to give the desired product **422** as a brown oil (0.53 mmol, 0.32 g 57%).

Novel

IR (ATR / golden gate): 3081 (w), 3062 (w), 3024 (w), 3002 (w), 2922 (w), 2835 (w), 1602 (m), 1495 (s), 1454 (s), 1435 (m).

^{1}H NMR (400 MHz, CHLOROFORM-*d*)

δ ppm 7.31–7.23 (6H, m, 6 x aromatic C**H**), 7.21–7.08 (7H, m, 7 x aromatic C**H**), 6.96 (1H, s, aromatic C**H**), 6.77 (1H, app. t, *J*=7.4 Hz, aromatic C**H**), 6.51 (1H, d, *J*=7.8 Hz, aromatic C**H**), 4.25 (2H, s, NC**H**$_2$Ar), 3.89 (3H, s, OC**H**$_3$), 3.69 (3H, s, OC**H**$_3$), 3.37 (2H, s, NC**H**$_2$), 2.70 (2H, app. td, *J*=12.9, 5.0 Hz, 2 x CH_2C**H**HPh), 2.50 (2H, app. td, *J*=12.9, 4.7 Hz, 2 x CH_2CH**H**Ph), 2.09 (2H, app. td, *J*=12.9, 5.0 Hz, 2 x C**H**HCH_2Ph), 1.98 (2H, ddd, *J*=13.2, 12.9, 4.7 Hz, 2 x CH**H**CH_2Ph).

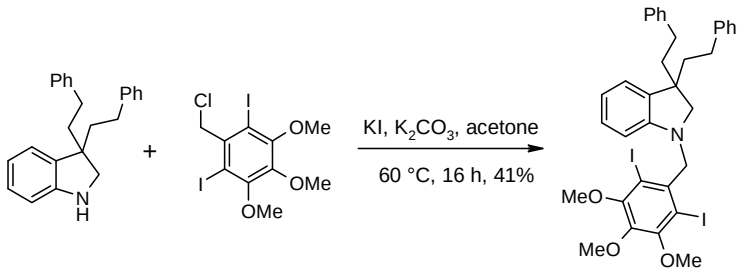
^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*)

δ ppm 151.9 (**C**), 149.7 (**C**), 148.8 (**C**), 142.7 (2x**C**), 135.1 (**C**), 132.8 (**C**), 128.6 (4x**C**H), 128.4 (4x**C**H), 128.1 (**C**H), 126.0 (2x**C**H), 123.2 (**C**H), 122.0 (**C**H), 118.1 (**C**H), 112.0 (**C**H), 107.2 (**C**H), 86.5 (**C**I), 63.8 (**C**H_2), 58.1 (**C**H_2), 56.4 (O**C**H_3), 56.0 (O**C**H_3), 47.7 (**C**), 41.7 (2x**C**H_2), 31.3 (2x**C**H_2).

ESMS: *m/z* (%): 604 $[M+H]^+$ (100), 626 $[M+Na]^+$ (90).

HRMS (ES +ve): $C_{33}H_{35}INO_2$ $[M+H]^+$ 604.1707, found 604.1694.

1-(2,6-Diiodo-3,4,5-trimethoxy-benzyl)-3,3-diphenethyl-2,3-dihydro-1*H*-indole (423).



421
$C_{24}H_{25}N$
(327.47)

395
$C_{10}H_{11}ClI_2O_3$
(468.46)

423
$C_{34}H_{35}I_2NO_3$
(759.47)

A solution of indoline **421** (0.61 mmol, 0.20 g), benzyl chloride **395** (0.51 mmol, 0.24 g), K_2CO_3 (3.06 mmol, 0.42 g) and KI (0.51 mmol, 85 mg) in acetone (30 mL) under argon was heated at reflux for 16 h. The reaction mixture was cooled to room temperature and partitioned between water (50 mL) and ether (50 mL). The aqueous phase was extracted with ether (2 x 30 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica, 5→25% diethyl ether in petroleum ether) to give firstly the desired product **423** as a brown oil (0.25 mmol, 0.19 g, 41%) and then the recovered starting material **421** (0.24 mmol, 80 mg, 40%).

Novel

IR (ATR / golden gate): 3081 (w), 3058 (w), 3020 (w), 2998 (w), 2926 (w), 2850 (w), 2824 (w), 1599 (m), 1486 (m).

^{1}H NMR (400 MHz, CHLOROFORM-*d*)

δ ppm 7.30–7.09 (12H, m, 12 x aromatic C**H**), 6.83–6.75 (2H, m, 2 x aromatic C**H**), 4.80 (2H, s, NC**H**$_2$Ar), 3.99 (3H, s, OC**H**$_3$), 3.95 (6H, s, 2 x OC**H**$_3$), 3.25 (2H, s, NC**H**$_2$), 2.67 (2H, app. td, *J*=13.0, 5.1 Hz, 2 x CH_2C**H**HPh), 2.48 (2H, app. td, *J*=13.0, 5.0 Hz, 2 x CH_2CH**H**Ph), 2.03 (2H, ddd, *J*=13.6, 12.2, 5.1 Hz, 2 x C**H**HCH_2Ph), 1.95 (2H, ddd, *J*=13.6, 12.2, 5.0 Hz, 2 x CH**H**CH_2Ph).

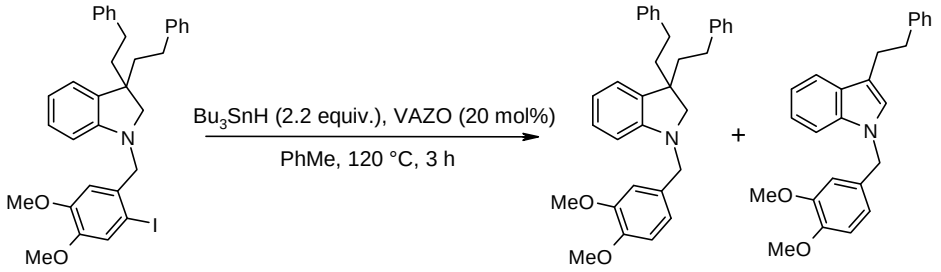
^{13}C NMR + DEPT (100 MHz, CHLOROFORM-*d*)

δ ppm 154.1 (2x**C**), 151.3 (**C**), 144.6 (**C**), 142.9 (2x**C**), 136.5 (**C**), 135.3 (**C**), 128.5 (8x**C**H), 127.8 (**C**H), 125.8 (2x**C**H), 123.1 (**C**H), 117.8 (**C**H), 107.4 (**C**H), 94.2 (2x**C**I), 61.9 (**C**H_2), 61.6 (**C**H_2), 61.2 (O**C**H_3), 61.0 (2xO**C**H_3), 47.4 (**C**), 41.3 (2x**C**H_2), 31.2 (2x**C**H_2).

ESMS: *m/z* (%): 760 $[M+H]^+$ (100), 782 $[M+Na]^+$ (50).

HRMS (ES +ve): $C_{34}H_{36}I_2NO_3$ $[M+H]^+$ 760.0779, found 760.0771.

1-(3,4-Dimethoxy-benzyl)-3,3-diphenethyl-2,3-dihydro-1*H*-indole (424) and 1-(3,4-Dimethoxy-benzyl)-3-phenethyl-1*H*-indole (425).



422
$C_{33}H_{34}INO_2$
(603.55)

424, 45%
$C_{33}H_{35}NO_2$
(477.65)

425, 6%
$C_{25}H_{25}NO_2$
(371.48)

To a solution of **422** (0.130 mmol, 80 mg) in toluene (10 mL) under argon was added tributyltin hydride (0.290 mmol, 0.08 mL) and VAZO (0.003 mmol, 6 mg). After 3 h at reflux the reaction mixture was cooled, concentrated *in vacuo* and purified by column chromatography (10% anhydrous K_2CO_3: 90% silica, 5% diethyl ether in petroleum ether) to give the firstly the fully reduced product (**424**) (0.059 mmol, 28 mg, 45%) as a colourless oil and then the indole (**425**) (0.008 mmol, 3 mg, 6%) as a colourless oil.

Date for **424**

Novel

IR (ATR / golden gate): 3054 (w), 3028 (w), 2930 (w), 2835 (w), 1603 (m), 1513 (m), 1489 (m), 1455 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.65–7.56 (5H, m, 5 x aromatic C**H**), 7.55–7.41 (8H, m, 8 x aromatic C**H**), 7.26 (1H, d, *J*=7.0 Hz, aromatic C**H**), 7.21 (1H, app. t, *J*=8.9 Hz, aromatic C**H**), 7.10 (1H, app. t, *J*=7.3 Hz, aromatic C**H**), 6.92 (1H, d, *J*=7.8 Hz, aromatic C**H**), 4.61 (2H, s, NC**H**$_2$Ar), 4.24 (3H, s, OC**H**$_3$), 4.16 (3H, s, OC**H**$_3$), 3.63 (2H, s, NC**H**$_2$), 3.00 (2H, app. td, *J*=12.8, 5.2 Hz, 2 x CH_2C**H**HPh), 2.82 (2H, app. td, *J*=12.8, 4.9 Hz, 2 x CH_2CH**H**Ph), 2.40 (2H, ddd, *J*=13.4, 12.8, 5.2

Hz, 2 x C**H**HCH$_2$Ph), 2.29 (2H, ddd, *J*=13.4, 12.8, 4.9 Hz, 2 x CH**H**CH$_2$Ph).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 152.3 (**C**), 149.3 (**C**), 148.3 (**C**), 142.8 (2x**C**), 135.3 (**C**), 131.2 (**C**), 128.5 (4x**C**H), 128.5 (4x**C**H), 128.0 (**C**H), 125.9 (2x**C**H), 123.3 (**C**H), 120.0 (**C**H), 117.8 (**C**H), 111.3 (**C**H), 110.9 (**C**H), 107.0 (**C**H), 63.4 (**C**H$_2$), 56.1 (O**C**H$_3$), 56.0 (O**C**H$_3$), 53.0 (**C**H$_2$), 47.5 (**C**), 41.6 (2x**C**H$_2$), 31.2 (2x**C**H$_2$)

ESMS: *m/z* (%): 478 $[M+H]^+$ (100), 500 $[M+Na]^+$ (30).

HRMS (ES +ve): $C_{33}H_{35}NNaO_2$ $[M+Na]^+$ 500.2560, found 500.2561.

Data for **425**

Novel

IR (ATR / golden gate): 3058 (w), 3024 (w), 2998 (w), 2933 (w), 2854 (w), 1607 (w), 1514 (m), 1463 (m), 1453 (m).

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

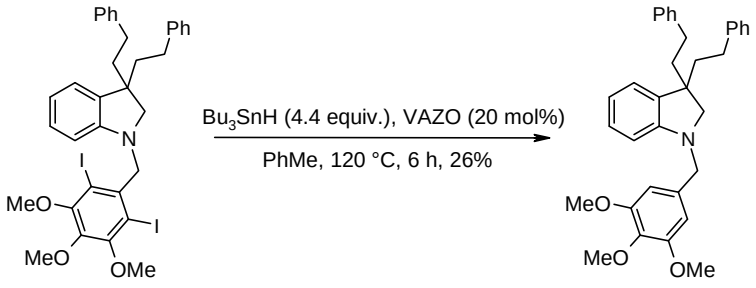
δ ppm 7.63 (1H, d, *J*=7.5 Hz, aromatic C**H**), 7.32–7.08 (9H, m, 9 x aromatic C**H**), 6.83 (1H, s, aromatic C**H**), 6.79 (1H, d, *J*=8.0 Hz, aromatic C**H**), 6.67 (1H, app. t, *J*=2.3 Hz, aromatic C**H**), 5.19 (2H, s, NC**H**$_2$Ar), 3.86 (3H, s, OC**H**$_3$), 3.79 (3H, s, OC**H**$_3$), 3.12–2.98 (4H, m, C**H**$_2$C**H**$_2$Ph).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 142.6 (**C**), 136.9 (**C**), 132.8 (**C**), 131.2 (**C**), 130.4 (**C**), 128.7 (2x**C**H), 128.5 (2x**C**H), 128.0 (**C**), 126.0 (**C**H), 125.6 (**C**H), 121.8 (**C**H), 119.5 (**C**H), 119.2 (**C**H), 119.1 (**C**H), 111.5 (**C**H), 110.5 (**C**H) 109.8 (**C**H), 56.1 (O**C**H$_3$), 56.1 (O**C**H$_3$), 49.9 (**C**H$_2$), 36.9 (**C**H$_2$), 27.5 (**C**H$_2$).

N.B. 1 x aromatic (**C**) not observed.

3,3-Diphenethyl-1-(3,4,5-trimethoxy-benzyl)-2,3-dihydro-1*H*-indole (426).



423
$C_{34}H_{35}I_2NO_3$
(759.47)

426
$C_{34}H_{37}NO_3$
(507.68)

To a solution of **423** (0.25 mmol, 0.19 g) in toluene (100 mL) under argon was added tributyltin hydride (1.10 mmol, 0.29 mL) and VAZO (0.05 mmol, 12 mg). After 16 h at reflux the reaction mixture was cooled, concentrated *in vacuo* and purified by column chromatography (10% anhydrous K_2CO_3: 90% silica, 5% diethyl ether in petroleum ether) to give the fully reduced product (**426**) (0.065 mmol, 33 mg, 26%) as a colourless oil.

Novel

^{1}H NMR (300 MHz, CHLOROFORM-*d*)

δ ppm 7.30–7.05 (12H, m, 12 x aromatic C**H**), 6.75 (1H, app. t, *J*=7.3 Hz, aromatic C**H**), 6.60 (2H, s, 2 x aromatic C**H**), 6.54 (1H, d, *J*=7.8 Hz, aromatic C**H**), 4.25 (2H, s, NC**H**$_2$Ar), 3.85 (3H, s, OC**H**$_3$), 3.79 (6H, s, 2 x OC**H**$_3$), 3.32 (2H, s, NC**H**$_2$), 2.67 (2H, app. td, *J*=12.9, 5.2 Hz, 2 x CH$_2$C**H**HPh), 2.47 (2H, app. td, *J*=12.9, 4.8 Hz, 2 x CH$_2$CH**H**Ph), 2.15–1.88 (4H, m, 2 x C**H**$_2$CH$_2$Ph).

^{13}C NMR + DEPT (75 MHz, CHLOROFORM-*d*)

δ ppm 153.6 (2x**C**), 152.2 (**C**), 142.7 (2x**C**), 137.1 (**C**), 135.2 (**C**), 134.5 (**C**), 128.6 (4x**C**H), 128.4 (4x**C**H), 128.1 (**C**H), 125.9 (2x**C**H), 123.3 (**C**H), 117.9 (**C**H), 107.0 (**C**H), 104.4 (2x**C**H), 63.5 (**C**H$_2$), 61.1 (O**C**H$_3$),

	56.2 (2xO**C**H_3), 53.4 (**C**H_2), 47.6 (**C**), 41.7 (2x**C**H_2), 31.3 (2x**C**H_2).
ESMS: *m/z* (%):	508 $[M+H]^+$ (100), 530 $[M+Na]^+$ (90).
HRMS (ES +ve):	$C_{34}H_{37}NNaO_3$ $[M+Na]^+$ 530.2666, found 530.2663.

References

1) Saxton, J. E. In *Indoles: The Monoterpenoid Indole Alkaloids*; John Wiley & Sons, **1983**, Vol. 25, pt. 4, 331-438.
2) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 995-1001.
3) Hesse, O. *Liebigs Ann*., **1882**, *211*, 249-282.
4) Kny, H.; Witkop, B. *J. Org. Chem*., **1960**, *25*, 635-637.
5) (a) Biemann, K. *J. Am. Soc. Mass Spectrom*, **2002**, *13*, 1254-1272. (b) Biemann, K.; Spiteller-Friedmann, M.; Spiteller, G. *J. Am. Chem. Soc*., **1963**, *85*, 631-638. (c) Schnoes, H. K.; Burlingam, A. L.; Biemann, K. *Tetrahedron Lett*., **1962**, *22*, 993-999. (d) Biemann, K.; Spiteller-Friedmann, M.; Spiteller, G. *Tetrahedron Lett*., **1961**, *14*, 485-492.
6) Gilbert, B. In *The Alkaloids*, Manske, R. H. F., Ed.; Academic Press: New York, **1965**, Vol. 8, 336-514.
7) Smith, G. F.; Wahid, M. A. *J. Chem. Soc.*, **1963**, 4002-4004.
8) Djerassi, C.; George, T.; Finch, N.; Lodish, H. F.; Budzikiewicz, H.; Gilbert, B. *J. Am. Chem. Soc.*, **1962**, *84*, 1499-1501.
9) de Araújo Jr., J. X.; Antheaume, C.; Traindade, R. C. P.; Schmitt, M.; Bourguignon, J. J.; Sant'Ana, A. E. G. *Phytochem. Rev*., **2007**, *6*, 183-188.
10) O'Conor, S. E.; Maresh, J. J. *Nat. Prod. Rep*., **2006**, *23*, 532-547.
11) Rahman, A. *Biosynthesis of Indole Alkaloids*, Oxford: Clarendon, **1983**, 95-127.
12) Stork, G.; Dolfini, J. E.; *J. Am. Chem. Soc.*, **1963**, 2872-2873.
13) Harley-Mason, J.; Kaplan, M. *Chem. Commun.*, **1967**, 915-916.
14) Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonamitsu, O.; Kanaoka, Y. *Tetrahedron Lett*., **1965**, *27*, 2261-2268.
15) Ban, Y.; Iijima, I.; *Tetrahedron Lett*., **1969**, *30*, 2523-2525.
16) Meyers, A. I.; Berney, D. *J. Org. Chem*., **1989**, *54*, 4673-4676.
17) Iyengar, R.; Schildknegt, K.; Aubé, J. *Org. Lett*., **2000**, *2*, 1625-1627.
18) Banwell, M. G.; Smith, J. A. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 2613-2618.
19) Sharp, L. A.; Zard, S. Z. *Org. Lett*., **2006**, *8*, 831-834.

20) Pearson, W. H.; Aponick, A. *Org. Lett*., **2006**, *8*, 1661-1664.

21) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem. Int. Ed*., **2007**, *46*, 6159-6162.

22) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem*., **1990**, *55*, 517-521.

23) Schultz, A. G.; Pettus, L. *J. Org. Chem*., **1997**, *62*, 6855-6861.

24) Tanino, H.; Fukuishi, K.; Ushiyama, M.; Okada, K. *Tetrahedron*, **2004**, *60*, 3273-3282.

25) Gallagher, T.; Magnus, P. *J. Am. Chem. Soc*., **1982**, *104*, 1140-1141.

26) Wenkert, E.; Hudlický, T. *J. Org. Chem*., **1988**, *53*, 1953-1957.

27) Forns, P.; Diez, A.; Rubiralta, M. *J. Org. Chem*., **1996**, *61*, 7882-7888.

28) Toczko, M. A.; Heathcock, C. H., *J. Org. Chem*., **2000**, *65*, 2642-2645.

29) Banwell, M. G.; Lupton, D. W. *Org. Biomol. Chem*., **2005**, *3*, 213-215.

30) Desmaële, D.; d'Angelo, J. *J. Org. Chem*. **1994**, *59*, 2292-2303.

31) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc*., **2002**, *124*, 4628-4641.

32) Laronze, P. J. Y.; Laronze-Fontaine, J.; Levy, J.; Le Men, J. *Tetrahedron Lett*., **1974**, *6*, 491-494.

33) Harley-Mason, J.; Ingleby, R. F. J. *J. Chem. Soc.*, **1958**, 3639-3642.

34) Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc*., **2002**, *124*, 13398-13399.

35) Patro, B.; Murphy, J. A. *Org. Lett*., **2000**, *2*, 3599-3601.

36) Ban, Y.; Honma, Y.; Oishi, T. *Tetrahedron Lett*., **1976**, *14*, 1111-1114.

37) Kinshita, H.; Ohnuma, T.; Oishi, T.; Ban, Y. *Chem. Lett.*, **1986**, 927-930.

38) Cartier, D.; Patigny, D.; Levy, J. *Tetrahedron Lett*., **1982**, *23*, 1897-1900.

39) Dufour, M.; Gramain, J. C.; Husson, H. P.; Sinibaldi, M. E.; Troin, Y. *Tetrahedron Lett*., **1989**, *30*, 3429-3432.

40) Le Menez, P.; Kunesch, N.; Liu, S.; Wenkert, E. *J. Org. Chem*., **1991**, *56*, 2915-2918.

41) Wenkert, E.; Liu, S. *J. Org. Chem*., **1994**, *59*, 7677-7682.

42) Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.*, **2001**, *30*, 94-103.

43) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.*, **1988**, *110*, 5900-5902.

44) Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.*, **1998**, 81-82.

45) Booth, S. E.; Benneche, T.; Undheim, K. *Tetrahedron*, **1995**, *51*, 3665-3674.

46) Wolf, H.; Gonzenbach, H.U.; Müller, K.; Schaffner, K. *Helv. Chim. Acta*, **1972**, *55*, 2919-2933.

47) Butula, I.; Kuhn, R. *Angew. Chem. Int. Ed.*, **1968**, *3*, 208-209.

48) (a) Lanzilotti, A. E.; Littell, R.; Fanshawe, W. J.; McKenzie, T. C.; Lovell, F. M. *J. Org. Chem.*, **1979**, *44*, 4809-4813, (b) Maryanoff, B. E.; McComsey, D. F. *J. Org. Chem.*, **1978**, *43*, 2733-2735.

49) Dainty, R. F., In *PhD Thesis, University of Southampton*, **1997**.

50) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.*, **1988**, *110*, 4796-4807.

51) Curran, D. P.; DeMello, N. C. *J. Chem. Soc., Chem. Commun.*, **1993**, 1314-1317.

52) Jones, K.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.*, **1992**, 1766-1767.

53) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N.C. *J. Am. Chem. Soc.*, **1994**, *116*, 3131-3132.

54) Booker-Milburn, K. I.; Fedouloff, M.; Paknoham, S. J.; Strachan, J. B.; Melville, J. L.; Voyle, M. *Tetrahedron Lett.*, **2000**, *41*, 4657-4661.

55) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn*., **1967**, *40*, 2380.

56) But, T. Y. S.; Toy, P. H. *Chem. Asian J*., **2007**, *2*, 1340-1355.

57) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem. Int. Ed*., **1999**, *38*, 3186-3189.

58) De Kimpe, N.; Stevens, C. *J. Org. Chem.*, **1993**, *58*, 2904-2906.

59) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 6041-6048.

60) Michael, J. P.; de Koning, C. B.; van der Westhuyzen, C. W.; Fernandes, M. A. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2055-2062.

61) Gómez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.*, **1996**, *118*, 8553-8565.

62) Harrowven, D. C.; Guy, I. L. *Chem. Commun.*, **2004**, 1968-1969.

63) Flanagan, S. R.; Harrowven, D. C.; Bradley, M. *Tetrahedron Lett*., **2003**, *44*, 1795-1798.

64) Sulser, U.; Widmer, J.; Goeth, H. *Helv. Chim. Acta*, **2004**, *60*, 1676-1690.

65) Torrado, A.; Imperiali, B. J. *Org. Chem*., **1996**, *61*, 8940-8948.

66) Rigby, J. H.; Laurent, S. *J. Org. Chem.*, **1998**, *63*, 6742-6744.

67) Ruiz, J.; Sotomayor, N.; Lete, E. *Org. Lett.*, **2003**, *5*, 1115-1117.

68) Daisley, R. W.; Walker, J. *J. Chem. Soc.*, **1971**, 1375-1379.

69) Nozoye, T.; Shibanuma, Y.; Nakai, T.; Hatori, Y. *Chem. Pharm. Bull.*, **1988**, *36*, 4980-4985.

70) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem. Int. Ed*., **2004**, *43*, 95-98.

71) Singh, R. P.; Majumder, U.; Shreeve, J. M. *J. Org. Chem.*, **2001**, *66*, 6263-6267.

72) Poondra, R. R.; Turner, N. *J. Org. Lett.*, **2005**, *7*, 863-866.

73) Schultz-Fademrecht, C.; Deshmukh, P. H.; Malagu, K.; Procopiou, P. A.; Barrett, A. G. *Tetrahedron*, **2004**, *60*, 7515-7524.

74) Zonjee, J. N.; de Koning, H.; Speckamp, W. N. *Tetrahedron*, **1989**, *45*, 7553-7564.

75) Padmavathi, V.; Venkata, S. D. R. C.; Balaiah, A.; Obula, R. B. C.; Padmaja, A. *Indian J. Chem. Sect. B*, **2005**, *44*, 2569-2574.

76) Tanikaga, R.; Nakayama, K.; Tanaka, K.; Kaji, A. *Chem. Lett.*, **1977**, 395-396.

77) Frigerio, M.; Santagostino, M. *Tetrahedron Lett*., **1994**, *35*, 8019-8022.

78) Torres, J. C.; Pinto, A. C.; Garden, S. J. *Tetrahedron*, **2004**, *60*, 9889-9900.

79) Rajswaran, W. G.; Cohen, L. A. *Tetrahedron*, **1998**, *54*, 11375-11380.

80) Ahmad-Junan, S. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 675-678.

81) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.*, **1991**, *56*, 4218-4223.